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Effects of Purple Coneflower (*Echinacea purpurea*) on CYP3A4 Metabolism and P-glycoprotein Mediated Transport *in Vitro*

Thesis for the degree of Philosophiae Doctor

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Rød solhatt (*Echinacea purpurea*) og effekt på cytokrom P-450 3A4 metabolisme og P-glykoprotein-transport *in vitro*

Solhatt har blitt et av de vanligste urtepreparatene på verdensmarkedet, og markedsføres for sin effekt mot luftveisinfeksjoner og forkjølelse. Sambruk av naturpreparater og legemidler forekommer ofte, og det er kjent at urtepreparater kan påvirke kroppens omsetning av legemidler. I verste fall kan konsekvensene være dødelige. Derfor er kunnskap rundt slike interaksjoner mellom urter og legemidler en viktig del av pasientsikkerheten.

Cytokrom P-450 3A4 (CYP3A4) er et spesifikt protein (enzym) som bidrar i omdanningen og nedbrytingen av ca 50% av alle markedsførte legemidler. P-glykoprotein er et transportprotein som bidrar til å transportere legemidler ut av kroppen eller redusere opptaket fra tarm. Begge disse proteinene kan påvirkes av urter slik at legemiddel-omsetningen og den kliniske effekten av legemidler kan endres (interaksjoner).

Hovedmålet med denne avhandlingen var å vurdere, gjennom ulike laboratorieteknikker, effekten av rød solhatt på CYP3A4 og P-glykoprotein, og å kartlegge eventuelle mekanismer til grunn for påvirkningen.

Solhatt viste i hovedsak en svak hemming av aktiviteten til P-glykoprotein. Samtidig fant vi at solhatt i noe større grad reduserte legemiddelnedbrytingen til CYP3A4. Effekten på CYP3A4 var forskjellig for ulike solhatt-produkter, men hovedtendensen var en svak hemming.

Det er generelt vanskelig å anslå den kliniske betydningen av laboratoriefunn alene. For hvert av de undersøkte proteinene er den hemmende effekten fra solhatt trolig liten, men vi vet at disse to proteinene virker samtidig, og en forsterket effekt i kroppen kan ikke utelukkes.

Mekanismene til grunn for hemmingen ble også studert. Studiene viste at solhatt har minst to ulike mekanismer for hemming av CYP3A4. Mekanismene var annerledes når solhatt var en del av et multi-preparat med andre urter som for eksempel svarthyll. Både for CYP3A4 og P-glykoprotein tyder de kompliserte hemmingsmekanismene på at to eller flere ulike substanser i solhatt-preparatet påvirker proteinet samtidig.

Det er verdt å merke seg at solhatt trolig er en ikke-reversibel hemmer av CYP3A4, som vil kunne gi en langvarig reduksjon i kroppens evne til å omsette legemidler, og dermed øke sjansen vesentlig for kliniske interaksjonseffekter med legemidler.

Samlet har vi vist at solhatt i beskjeden grad påvirker CYP3A4 og P-glykoprotein i laboratorieforsøk. Vi har ikke grunn til å tro at den kliniske effekten er av vesentlig betydning. På bakgrunn av en ikke-reversibel hemming av CYP3A4 kan vi likevel ikke bedømme solhatt som ufarlig med tanke på klinisk interaksjonsrisiko. Selv om vi ikke kan gi klinisk konklusive svar, har studiene brakt frem mer kunnskap omkring solhatts påvirkning på legemiddelomsetningen og om legemiddel-urt-interaksjoner generelt.

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Tønsberg/Trondheim, September 2012

Torstein Schrøder-Aasen

Abbreviations

A-B	Apical to basolateral
ATP	Adenosine triphosphate
B-A	Basolateral to apical
BFC	7-benzyloxy-trifluoromethylcoumarin
BG	Bergamottin
BQ	7-benzyloxyquinoline
cDNA	Complementary deoxyribonucleic acid
CPM	Counts per minute
CYP	Cytochrome P-450
CYP3A4	Cytochrome P-450, subtype 3A4
Da	Dalton (molecular mass)
DBG	6'7'-dihydroxybergamottin
DPM	Disintegrations per minute
HFC	7-hydroxytrifluoromethylcoumarin
HQ	7-hydroxyquinoline
IC_{50}	Inhibitor concentration reducing the enzyme activity by 50% compared to control activity
J_{Net}	Net digoxin flux
K_i	Inhibition constant
K_m	Michaelis Menten constant for a substrate (the substrate concentration at which ½ × V_{max} occurs)
MDR	Multidrug resistance
$MgCl_2$	Magnesium chloride
$NADP^+$	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
OATP	Organic anion transporting polypeptides
P_{app}	Apparent permeability coefficient
P-gp	P-glycoprotein
SD	Standard deviation

TEER	Transepithelial electric resistance
UV	Ultraviolet
V_{max}	The maximum enzyme activity rate
QC	Quality control

Table of Contents

List of Papers

This thesis is based on the following publications:

Paper I

Torstein Schrøder Hansen and Odd Georg Nilsen.
Echinacea purpurea and P-Glycoprotein Drug Transport in Caco-2 Cells. *Phytotherapy Research* 2009; 23: 86-91

Paper II

Torstein Schrøder Hansen and Odd Georg Nilsen.
In vitro CYP3A4 Metabolism: Inhibition by *Echinacea purpurea* and Choice of Substrate for the Evaluation of Herbal Inhibition. *Basic and Clinical Pharmacology and Toxicology* 2008; 103: 445-449

Paper III

Torstein Schrøder-Aasen, Guri Molden and Odd Georg Nilsen.
In vitro Inhibition of CYP3A4 by the Multiherbal Commercial Product Sambucus Force and its Main Constituents *Echinacea purpurea* and *Sambucus nigra*. *Phytotherapy Research* 2012; Published online 8.feb 2012; DOI 10.1002/ptr.4619

Summary of Papers

Paper I

Echinacea purpurea and P-glycoprotein Drug Transport in Caco-2 cells.

The main objective of this study was to evaluate the *in vitro* inhibitory potential of *Echinacea purpurea* on the P-glycoprotein (P-gp) mediated transport of digoxin in human intestinal Caco-2 cells. The bi-directional transport of radiolabeled ^{3}H-digoxin through Caco-2 cell membranes was measured in the presence or absence of *E. purpurea* extract or the positive control inhibitor verapamil. Liquid scintillation counting was used for quantification of radiolabeled digoxin.

A statistically significant linear dose-related decrease in net digoxin flux was observed in presence of *E. purpurea* concentrations from 0.4 to 6.36 mg/mL, indicating a dose-dependent *E. purpurea* inhibition of P-gp. Up to 22.3% decreased transport was measured at the highest *E purpurea* concentration possible to reach. At lower *E. purpurea* concentrations, a minor increase in net digoxin flux was observed. This effect is suggested to be caused by allosteric site activation, and the observed dual effect by *E. purpurea* could be a result of the complex composition of the herbal extract.

The calculated V_{max} and K_m values for P-gp digoxin transport were in the same range as reported by others, and the influence from *E. purpurea* was in concordance with an uncompetitive inhibition.

The net digoxin flux was decreased by 18% in presence of 0.8% ethanol, needed for herbal extraction and compatibility with the commercial product studied. This indicates a significant P-gp inhibition potential by lower ethanol concentrations. Verapamil, the positive inhibition control, decreased the net digoxin flux by 75%.

It is concluded that the influence of *E. purpurea* on P-gp activities *in vivo* probably are limited, although the possibility of effects on drug bioavailability can not be excluded.

Paper II

In vitro CYP3A4 metabolism: Inhibition by Echinacea purpurea and choice of substrate for the evaluation of herbal inhibition.

The main objective of this study was to compare the CYP3A4 inhibition profiles of *Echinacea purpurea,* St. John's wort and ketoconazole when measured with different substrates and methodologies. A secondary objective was to further evaluate the inhibitory potential of *E. purpurea* towards CYP3A4 *in vitro*.

The CYP3A4 metabolism of 7-benzyloxy-trifluoromethylcoumarin (BFC), 7-benzyloxyquinoline (BQ) and testosterone was measured with fluorescence- or HPLC-based assays in presence and absence of herbal extract or the known CYP3A4 inhibitor ketoconazole.

The study confirms an inhibitory potential of *E. purpurea*, St. John's wort and ketoconazole on CYP3A4 as reported in other studies. For both St. John's wort and ketoconazole, the assays showed inhibitory profiles with a reasonably high concordance for all three substrates. In the presence of *E. purpurea*, the CYP3A4 metabolism of testosterone was less inhibited (IC_{50}: 5394 µg/mL) compared to BFC and BQ metabolism (IC_{50}: 354 and 452 µg/mL, respectively). However, the same rank order of CYP3A4 inhibition potential was observed for all substrates, ketoconazole being the most potent and *E. purpurea* the least potent of the inhibitors.

It is discussed whether the complex composition of *E. purpurea* with its different constituents may, at least partly, explain the divergence in its inhibitory profiles compared to St. John's wort and ketoconazole. As the three substrates bind to different binding sites on the CYP3A4 enzyme, the *E. purpurea* constituents might exert distinctive effects on the different binding sites. It is, however, not possible to exclude that the different quantification techniques may also be responsible for the variation observed for *E. purpurea* inhibition. Consequently, the choice of substrate and quantification methodology might be essential for the evaluation of herbal inhibition of CYP3A4 metabolism.

The inhibitory potency of *E. purpurea* was found to agree with other previous studies, reporting *E. purpurea* as a relatively weak inhibitor of CYP3A4 *in vitro*.

Paper III

In vitro inhibition of CYP3A4 by the multiherbal commercial product Sambucus Force and its main constituents Echinacea purpurea and Sambucus nigra.

The aims of the study in paper III were to evaluate Sambucus Force's inhibition potential and inhibition mechanisms towards CYP3A4, and to evaluate the inhibitory co-contribution of the two main constituents *Echinacea purpurea* and *Sambucus nigra*.
Metabolic studies were performed with human recombinant CYP3A4, using testosterone as substrate, in presence or absence of Sambucus Force, *E. purpurea* or ketoconazole (positive inhibition control). A validated HPLC method was used for quantification of metabolite. The study included metabolic assays for the measurement of half maximal inhibitory concentration (IC_{50}), estimation of pharmacokinetic parameters (V_{max}, K_m and K_i) and identification of possible mechanism-based inhibition.
Sambucus Force inhibited CYP3A4 activity with a mean (95% confidence interval) IC_{50} value of 1192 (1091-1302) µg/mL. As a single herb, *E. purpurea* showed an IC_{50} value of 121.5 (114-119). When the IC_{50} values were converted to express the corresponding amount of dried *E. purpurea* raw-plant material used in production of each product, no significant difference was found between the IC_{50} equivalent values for the two products. Thus, the inhibitory potency of Sambucus Force seems exclusively to be exerted by *E. purpurea*, implicating an insignificant inhibition by *S. nigra*.
The inhibition by *E. purpurea* as single herb was in agreement with a mechanism-based inhibition with heterotropic positive cooperative effects. *Echinacea purpurea* acted differently as part of Sambucus Force, which showed a dual inhibition profile with both a time-dependent (substrate-independent) inhibitory mechanism and an uncompetitive (substrate-dependent) inhibition. The observed mechanistic differences are suggested to be caused by herb-herb-interactions in the multiherbal product.
The CYP3A4 inhibition of Sambucus Force *in vitro* is considered relatively weak, but the manufacturer's high recommended herbal dosages might enhance the potential for clinical interactions.

1. Introduction

1.1 Herbal Medicine

Herbs and plant material have been used by man for thousands of years for treatment of disease and alleviation of symptoms. Archeological evidence indicates the use of medicinal plants from prehistoric times, and healing with medicinal substances is subject in some of our earliest written records[1].

The ancient Egyptians of 3000 to 6000 years ago administered a variety of drugs obtained from natural resources, and they are credited with the early medicinal use of opium, castor oil and mints[1]. The ancient Greeks of 1500 to 3000 years ago continued the development of plant-based therapeutic health care. According to written records, the Greek philosopher Hippocrates, later to be known as the father of modern medicine, recommended pain alleviation through chewing willow leaves, which later have shown to contain salicylic acid[2]. In the historic cultures in China, Tibet and India from 1000 to 2000 years ago, the herbal specialists were powerful and influential professionals. Further into the continuing centuries and through the middle age, herbal medicine served as a basis for the medical practice.

The last two centuries have brought substantial change to medical practice. The evidence-based practice has been established as a fundament for the medical profession, and the majority of medical preparations are today produced synthetically by pharmaceutical companies. However, many of our extensively used drugs in today's evidence-based medicine were first identified from plants. Morphine, used against severe pain, was discovered from the opium poppy (*Papaver somniferum*). Digoxin and digitoxin, used in patients with congestive heart failure and arrhytmia, were first extracted from the plant Common foxglove (*Digitalis purpurea*). The anti-malarial drug quinine was derived from the bark of the Cinchona tree (*Cinchona officinalis*)[1]. Thus, the herbal medicine has in many ways served as a basis for the development of the modern pharmaceutical practice.

Even today, herbal medicine has an important place in modern cultures. Especially in Asia and in the developing world, with higher poverty rates and fewer medicinal doctors, the herbal and traditional medicine is still popular and an important part of the primary health care. In the western world, a division has developed between a modern evidence-based medicine on one side and a complementary and alternative medicine on the other side. The alternative direction has gained a high popularity, partly because alternative medicines, including herbal preparations, are regarded as more "natural" with fewer side effects than synthetically produced preparations.

1.2 Use of Herbal Preparations in the Population

The use of herbal products as alternative and complementary therapy has increased considerably in the Western world during the last decades. Studies from the United States have reported that the prevalence in use of herbal medicines among adults increased from 2.5% in 1990 to 12.1% in 1997[3]. A study of more than 30,000 adults in the United States reported a further increase to 18.6% in 2002[4], and a similar study found a prevalence of 17.7% in 2007[5]. The latter study further reported the prevalence of herbal use among children to be 3.9%. However, the prevalence varies across the world, exemplified by a Malaysian study reporting a prevalence of 33.9% among adults[6].

In terms of sales, the area of herbal medicines has become a billion dollar industry. Eisenberg *et al.* (1998) estimated the sales of herbal therapies in the United States in 1997 to be $5.1 billion[3]. More recently, a study from 2007 based on a survey of more than 23,000 participants, estimated the sales of natural products in the United States to be $14.8 billion[7], whereas a different study mainly based on manufacturer and retailer information estimates the 2010 herbal sales in the United States to be $5.2 billion[8]. There is reason to believe that the sales figures are similar in the comparable industrialized countries.

1.3 The Risk of Herb-Drug Interactions

It is a major problem of the extensive herbal use that many of the herb consumers are medicated with conventional drugs as well. Drug-drug interactions have been acknowledged as a safety challenge in the medical practice for a relatively long time, but the risk of herb-drug-interactions has for several reasons been approached to a lesser extent. This is probably due to several reasons:

1. Herbal products are usually marketed as dietary supplements and are therefore not subject to the standardized safety evaluation to the same extent as registered drugs[9].
2. The herbal products often include a wide range of constituents, and each of these may influence differently on the metabolism enzymes and transport proteins, making results harder to interpret and clinical effects more difficult to predict.
3. There are reports of significant lot-to-lot variation of active ingredient amounts, and herbal products from retail stores often do not contain the labeled species[10].
4. The public has regarded herbal products as more safe than synthetic drugs due to their natural origin, and the medical community has probably not recognized the risk of interactions due to the lack of scientific evidence of effects in treatment.

As a consequence, the use of some herbs has shown unforeseen effects when used in combination with other drugs. For example, the use of St. John's wort in treatment of depressive symptoms has shown to induce life-threatening rejection of transplanted organs when consumed under medication with cyclosporine[11]. Furthermore, the concomitant use of St. John's wort and oral contraceptives has been shown to significantly increase break-through bleedings and the possibility of unwanted pregnancies. In detail, St. John's wort has been found to modulate the effects of the metabolism enzyme Cythocrome P-450 3A4 (CYP3A4), both *in vitro*[12] and *in vivo*[13]. In a clinical situation, St. John's wort has been found to cause an induction of CYP3A4, resulting in increased clearance of drugs which are CYP3A4 substrates. Subsequently, when the lowered drug concentration drops below its therapeutic level, the drug does not longer work according to the intentions. The consequences can be fatal if the drug is a vital necessity, and the risk of significant clinical interactions is considerably

enhanced when the drug has a narrow therapeutic range, of which the immunosuppressant drug cyclosporine is a good example of both.

Pharmacokinetic interactions involve a remedy changing the absorption, distribution, metabolism and/or excretion of a substance, causing a change in the drug's concentration in the body or in a defined distribution volume. The three main systems of importance are 1) metabolism by the Cytochrome P-450 system, 2) trans-membrane drug transport by P-glycoprotein and 3) the binding of drugs to plasma proteins. The former two systems are addressed in the *in vitro* studies of this thesis, and are further discussed in the following chapters.

In the years since the case reports about St. John's wort[11], there has been a growing attention on herbal interactions, and many papers considering herb-drug-interactions have been published during the last decade. Grapefruit juice is now well known for its interactions with both cytochrome P-450 drug metabolizing enzymes and P-glycoprotein[14], and several popular herbs such as garlic, ginkgo, saw palmetto, milk thistle and ginseng have been studied and reviewed with varying results[15;16].

However, herbs are mainly investigated *after* they have been marketed and gained popularity, and there is still a long way to go before the pharmacokinetic interactions of herbal products are systematically evaluated. This is certainly of importance as 16 to 20% of all patients on regular medication have been reported to take herbal preparations, usually without the knowledge of their physician[17;18].

1.4 *Echinacea purpurea*

Echinacea is a genus of hardy, perennial wildflower plants, native to parts of the North American prairie, and more commonly known as purple coneflower. Of nine Echinacea species, *Echinacea purpurea*, *Echinacea angustifolia* and *Echinacea pallida* are the three usually used as herbal medication, although it has been debated whether *E. angustifolia* and *E. pallida* are variances of one species[19]. The Native Americans were

the first to use Echinacea for medical purpose, ranging from sore throats to snake bites[20]. The European settlers learned about its use, and Echinacea gained great popularity in the late 19th and early 20th century, alleged to cure syphilis, malaria, gangrene, diphtheria and mad dog disease, and concurrently being perfectly harmless[21]. In 1909, the American Council of Pharmacy and Chemistry declared in the reputable JAMA journal that Echinacea was to be "considered valueless", lacking "any scientific scrutiny" of the medicinal claims, and was "deemed unworthy of further consideration" until reliable favourable evidence was presented[21]. The popularity fell along with the great medical improvement and progress of antibiotics. Nevertheless, the use of Echinacea continued to some extent, and during the 20th century, *E. purpurea* was brought to Europe where it is now widely cultivated[22].

Along with the advancement of herbal medicine during the last decades, Echinacea has established a position as a top-selling herb on the Western herbal market. During the 1990s, more than 2 million physicians' prescriptions for Echinacea were filled each year[23]. Echinacea became the top-selling herb in the United States in 1995 and 1996[24], representing about 10% of the total herbal sales. A major health survey from 2007 reported Echinacea as the most used herb among both adults and children, estimated to more than 4.8 million consumers in the United States[5]. In recent years, the market has somewhat declined, but Echinacea was in 2010 still placed sixth on the United States mainstream market[8].

Today's use is mainly based on Echinacea's alleged effects for preventing and treating upper respiratory infections and the common cold, and immunostimulatory mechanisms have been proposed[22]. Groups of Echinacea chemical constituents such as alkylamides and caffeic acid derivatives have been considered important for Echinacea's activity[19]. The clinical evidence is widely discussed, and the latest Cochrane review on Echinacea's effects against the common cold concludes that clinically beneficial effects might exist, but the evidence is inconsistent[25].

Hundreds of commercial products are available in preparations such as liquid extracts, juices, capsules, tablets, dried plant material, creams, gels and tea. Furthermore,

different parts of the plants are used, including root, seeds, leaves and flower. The liquid extract of *E. purpurea* is the most commonly used preparation in the United States[20].
A study from 2003 reported that the labeling of marketed *E. purpurea* products was frequently inaccurate, and 10% of the preparations studied contained no trace of Echinacea[10]. This significant phytochemical diversity represents a major challenge in the comparison of pharmacological and clinical effects by Echinacea products[19;25].

1.5 Cytochrome P-450 System and CYP3A4

The cytochrome P-450 (CYP) superfamily is a large and functionally diverse group of heme-containing proteins, named for their cellular ("cyto") location and spectrophotometric characteristics ("chrome") with a spectral absorbance peak at 450nm wavelength when bound to carbon monoxide. CYP proteins have been found in every major domain of living organism, including bacteria, fungi, plants, insects and mammals[26]. Among several thousand identified CYP proteins in different species, 57 genes coding for CYP-enzymes have been identified in the human genome[27].

In humans, CYP proteins are predominately known for their role as phase I enzymes in the xenobiotic and drug metabolism. Their main function is to introduce hydroxyl groups at relatively inert structures such as hydrocarbons and aromatic rings[26]. The hydroxyl group makes the molecules more hydrophilic, and makes the substances more susceptible for conjugation, further degradation and excretion. In this reaction, molecular oxygen is split, giving one oxygen atom to the hydroxyl group while the other is released as part of a water molecule. This reaction further requires two reducing equivalents from an electron donor, usually from NADPH. The reactions are summarized by the equation

$$SH + O_2 + NADPH + H^+ \rightarrow SOH + NADP^+ + H_2O \qquad \text{(equation I)}$$

where SH is the substrate and SOH is the oxidized product[26]. It should be mentioned, however, that this transformation is generally complex, involving a series of sequential steps, and reactive intermediates can be bound and released at different steps along the

catalytic cycle. In addition to the hydroxylation, CYP enzymes also catalyze reactions such as epoxidations, dealkylations and deaminations.

Human CYP enzymes are not only involved in xenobiotic degradation. The catalyzed oxidation can convert substances to physiologically active products, a process called bioactivation. Examples of such include the conversion of pro-drugs to pharmacologically active molecules, and the conversion of pro-carcinogens to carcinogenic substances. Furthermore, CYP enzymes in human have key roles in the steroidogenesis, fatty acid metabolism and vitamin D metabolism[26].

In the CYP mediated metabolism of drugs, about 95% of the drugs are metabolized via only five of these enzymes, namely CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4[27]. Although accounting for a fewer number of drugs, CYP1A1, CYP2B6 and CYP2E1 should be mentioned. The CYP enzymes are predominately localized in the liver, where the majority of drug metabolizing activities are concentrated, but CYP enzymes are found in substantial amounts in other tissues as well, such as the brain, gastrointestinal tract, lungs and kidneys[26].

1.5.1 Variance in CYP Metabolic Activity Rates

1.5.1.1 Genetic Polymorphisms

The human CYP genes show a high degree of genetic polymorphism. While some individuals are lacking functional genes for certain CYP alleles, others have several active genes for the same allele, resulting in a significant variation in levels of expressed CYP enzyme and, thus, metabolic activity[28]. Although nearly all xenobiotic-metabolizing CYPs are polymorphic, this phenomenon is best known for CYP2D6[28]. About 6% of Caucasians have been found to be CYP2D6 poor metabolizers, with subsequent significant impact on the *in vivo* metabolism of common pharmaceuticals, e.g. metoprolol and codeine[26]. On the other hand, ultra-rapid CYP2D6 metabolizers are found mainly in ethnic groups from North-Africa and Oceania[28].

1.5.1.2 Induction and Activation

While genetic polymorphisms principally are congenital attributes, environmental factors, among them xenobiotics, may play important roles by influencing the activity of CYPs. The induction of CYP synthesis is a protective cellular mechanism where the xenobiotic presence triggers a cellular response involving activation of nuclear receptors, which in turn increase the gene expression and production of CYP enzymes, again resulting in increased clearance of xenobiotics[29]. This process is relatively slow, generally requiring xenobiotic presence over time, which occurs with multiple or regular drug use. The clinical consequence is decreased plasma concentrations of substrate drugs, which may reach sub-therapeutic levels and thus therapeutic failure. In the case of pro-drugs and pro-carcinogens, induction will result in *increased* levels of active metabolites and carcinogens, respectively. Increased metabolism may also arise from activation of existing CYP enzymes, as in the case of allosteric cooperative regulation of CYP-activity[30].

1.5.1.3 Inhibition

Inhibition of enzymes can occur in a number of ways, and the main differentiation is between reversible and irreversible inhibitors. The reversible inhibition is the most common, and is further categorized as competitive, non-competitive, uncompetitive and mixed-type inhibition. When the inhibitor molecule and enzyme's substrate competes for the same binding spot in the enzyme's active site, the inhibition is characterized as *competitive* inhibition. *Non-competitive* inhibition occurs when the inhibitor binds to sites distinctly different from the substrate, but still blocks the enzyme's turnover. *Uncompetitive* inhibition is a more special case where the inhibitor does not bind to the free enzyme, but only to the enzyme-substrate complex[31]. When both competitive and non-competitive elements of inhibition are seen, the inhibition is categorized as *mixed-type*.

The irreversible *mechanism-based* inhibition is characterized by the CYP-mediated metabolism of a xenobiotic compound, producing a reactive metabolic intermediate which is able to bind irreversibly to the CYP enzyme causing irreversible inhibition[32].

The irreversibly inactivated enzymes need to be re-synthesized through protein synthesis before normal activity is restored, causing a prolonged reduction of metabolic clearance even after elimination of the inactivator[33]. Because the catalytic step is necessary, such inhibition will show both NADPH-dependency and time-dependency in *in vitro* assays[32].

1.5.2 CYP3A4

In the cytochrome P-450 superfamily, the CYP3A4 is probably the most important drug-metabolizing CYP enzyme, and has been estimated to be involved in the metabolism of about 50% of marketed drugs[26;34]. CYP3A4 is by far the most abundant CYP enzyme in the human liver, but is also significantly expressed in the human small intestines, where it plays an important role in the drug metabolism[26;35].

The pharmacokinetics of CYP3A4 has shown to be complex. Firstly, CYP3A4 has probably the broadest substrate specificity of any CYP, with its substrates ranging in molecular mass from 151 g/mol (paracetamol/acetaminophen) to 1202 g/mol (cyclosporine). Secondly, CYP3A4 has shown homotropic and heterotropic cooperativity, where the enzyme activity is directly modulated by the presence of substrate itself or another compound, respectively. Furthermore, the existence of multiple binding domains within the active site of the CYP3A4, together with the possibility of multiple substrate molecules bound simultaneously, has been strongly suggested[36;37].

A wide range of xenobiotics have shown to interact with CYP3A4, to a greater or lesser extent. This includes also several of the CYP3A4 substrates. Examples of CYP3A4 interactive drugs are the strong inhibitors *ketoconazole* (antimycotic) and *clarithromycin* (antibiotic)[38;39], and the inducers *carbamazepine* (antiepileptic) and *rifampicin* (antituberculosis)[39;40]. In the area of natural products, the strong CYP3A4 inhibition by *grapefruit juice* and induction by *St. John's wort* are relatively well known[14;16]. The interaction potential with CYP enzymes is now subject to evaluation in

the development of new drugs. However, herbal medicines are not subject to the thorough evaluation procedures as with medical drugs, and the possibility of herbal interactions has, until recently, been relatively unknown.

1.6 P-glycoprotein

P-glycoprotein (P-gp) is a 170 kDa energy-dependent transmembrane efflux transporter driven by ATP hydrolysis. The main function of the MDR1-gene encoded P-gp is to actively transport its substrates out of the cell. P-gp is mainly localized in the intestinal epithelium, kidney tubules, placenta, blood-brain-barrier and liver hepatocytes, among other tissues[41;42].

P-gp has proven to have an important role in pharmacological distribution of drugs in the human body[43]. Due to its location in the apical cell membrane of enterocytes, it exports its substrates to the intestinal lumen (figure 1)[43]. As many of the P-gp substrates are toxic to the human body, the P-gp helps in detoxification by reducing the peroral absorption and thus the intracellular concentration of drugs. Likewise, the P-gp in apical placenta and blood-brain barrier protects the foetus and brain, respectively, from the uptake of possible toxins. In the liver and kidneys, however, P-gp is mainly located to the biliary cell membrane of hepatocytes and the apical side of proximal tubular epithelium, respectively[42]. Thus, P-gp also actively enhances the elimination of its substrates from the human body.

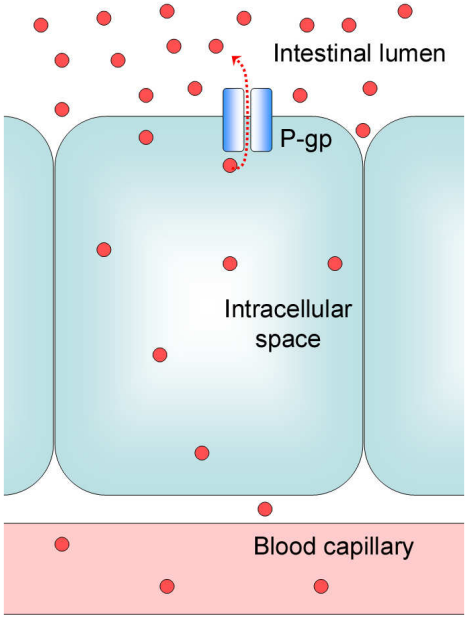

Figure 1. Schematic illustration of an intestinal epithelial cell, expressing P-gp. The efflux transport activity of the P-gp lower the intracellular drug concentration, thus resulting in a lower drug concentration in the blood stream.

As CYP3A4, the P-gp has broad substrate specificity, and a significant overlap between P-gp and CYP3A4 substrates has been reported[44]. P-gp and CYP3A4 are closely co-located in the small intestines, which has led to the hypothesis that they act synergistically. Due to the active efflux by P-gp, the xenobiotic substrate molecules may cross the apical cell membrane several times before they may access the blood stream. As a result, the xenobiotic's presence in the intestinal tissue is prolonged, where it can be metabolized by the intestinal CYP3A4. This theory has been supported by *in vitro* and *in vivo* experimental studies[45;46].

P-gp has shown to be a subject for pharmacokinetic interactions. Inhibition of P-glycoprotein reduces the efflux of drugs, and thereby leads to increased systemic drug concentrations, with possible adverse or toxic reactions. In opposite, induction will decrease the systemic drug levels, risking a loss of therapeutic effects. In human, the cardiac drug *verapamil* has shown to increase serum digoxin concentrations, causing symptoms of digoxin toxicity, as a result of P-gp inhibition[47;48]. Similarly, the

antituberculosis drug *rifampicin* has shown to be an inducer of P-gp[49]. The important role of P-gp in drug pharmacokinetics has made bi-directional transport studies to a routine screening in the drug development process[50].

2. Aims of the Thesis

Echinacea purpurea has been among the top-selling herbs in an increasing herbal market, but knowledge about its possible pharmacokinetic interaction potential is limited.

The main purpose of this thesis was to gain further knowledge about the *in vitro* pharmacokinetic inhibition potential and mechanisms of *E. purpurea* towards CYP3A4 and P-glycoprotein.

The following questions were addressed:

- Does *E. purpurea* inhibit P-glycoprotein mediated efflux transport *in vitro*?
- Does *E. purpurea* inhibit CYP3A4 mediated metabolism *in vitro*?
- Does the choice of substrate and experimental methodology influence on the inhibition patterns of *E. purpurea* on CYP3A4?
- What type of inhibition is exerted on CYP3A4 by *E. purpurea*?
- Is *E. purpurea* a mechanism-based inhibitor of CYP3A4?
- What is the inhibitory contribution of *E. purpurea* towards CYP3A4 when being part of a multiherbal preparation?
- Do our *in vitro* data indicate that *E. purpurea* represents a significant risk for pharmacokinetic drug interactions *in vivo*?

3. Methods

Several different methods were used in the work behind the present thesis. General considerations on these procedures are given below. Further details are described in detail in each paper.

3.1 Herbal Preparation

The commercial herbal products used in the experiments were obtained from the public market in local pharmacies and healthcare shops. Two different liquid ethanol extracts of *E. purpurea* were assessed; Echinagard® (Madaus AG, Germany) and Echinaforce® (A. Vogel, Bioforce AG, Switzerland). For preparation, liquid aliquots were transferred to pre-weighed vials, evaporated to dryness, and reweighed. The weight of dried extract was used as basis for the denomination of *E. purpurea* concentration in further solutions. Dried extract was re-dissolved in the smallest possible volume of water or 20% ethanol to give stock solutions of high concentrations.

St. John's wort (Hypericum Stada®, Stada Arzneimittel AG, Germany) and the multiherbal Sambucus Force (Nature's Sunshine Products Inc., USA) were bought as dried, capsular preparations. One capsule was dissolved for extraction in water or 20% ethanol as previously described for our laboratory[51]. Extract was then transferred to pre-weighed vials, evaporated, reweighed and further re-dissolved as described for *E. purpurea*.

The final herbal concentrations were anticipated to cover the *in vivo* concentrations of the herb, based on the recommended daily dose dissolved in 1 liter of gastrointestinal fluid or 56 liters of total body fluid. When ethanol was present in the herbal solutions, the final ethanol concentration caused by herbal addition was kept constant through all experiments.

3.2 CYP Incubations

The CYP3A4 enzymes were obtained as a commercial product (BD Supersomes™, BD Biosciences, USA). In production, the enzymes were prepared from insect cells which were infected with a baculovirus expressing the recombinant human cDNA for the specific enzyme. The commercial product further contained supportive reductase enzyme and cytochrome b5, aiding in the redox-activities of the CYP3A4.

In this work, the inhibition of CYP3A4 was evaluated with different CYP3A4 substrates. Incubations with the two substrates 7-benzyloxy-trifluoromethylcoumarin (BFC) and 7-benzyloxyquinoline (BQ) were performed on microtiter plates with a commercial CYP3A4 test kit. All test reagents were supplied with the commercial kit, and the manufacturer's procedure instructions were followed. The CYP3A4 concentration was 5.0nM with BFC (50µM) as substrate, and 7.5nM with BQ (40µM) as substrate. All incubations included a NADPH regenerating system consisting of 1.25mM $NADP^+$, 3.3mM glucose-6-phosphate, 3.3mM $MgCl_2$, 0.4U/mL glucose-6-phosphate dehydrogenase and 0.05mM sodium citrate. Serial dilutions of *E. purpurea* and St. John's wort extracts were added, and ketoconazole was supplied in the commercial kit as positive inhibition control. With BFC and BQ as substrates, ethanol extracts of herbs were used, and all incubations therefore included 0.8% final ethanol concentration. The total incubation time was 30 minutes, and the microtiter plates were inserted in a fluorometer for quantification of metabolite.

The assays with testosterone as substrate were performed in glass tubes in total volumes of 400µL, containing 20nM CYP3A4 and 0.1mM testosterone. The NADPH-regenerating system was present in identical concentrations as for the BFC and BQ assays. Various concentrations of *E. purpurea*, St. John's wort or Sambucus Force extracts were added, and ketoconazole was used as positive inhibition control. When ethanol extracts of herbs were used, all incubations in the assays included 0.8% final ethanol concentration. All incubation mixtures were equilibrated for 5 minutes in a gently shaking 37°C water bath before incubations were initiated. The incubations were

stopped after 10 minutes by addition of ice cold methanol, and after centrifugation, the supernatant could be applied directly to HPLC-vials for metabolite quantification.

3.3 Cell Membrane Transport Studies

3.3.1 Cell Cultivation

The Caco-2 cell line, derived from a human colorectal adenocarcinoma, differentiates to a polarized monolayer when cultivated on semi-permeable membranes, expressing several characteristics of an intestinal enterocyte membrane[52]. The Caco-2 membranes have been shown to express P-glycoprotein[53], and the use of Caco-2 cells is now a well established method for evaluation of P-gp-mediated transport[50]. The cells were first cultivated to passage 35-45, and during these passages seeded in 24-well 6.5mm Transwell® plates with 0.4µm Pore Polycarbonate Membrane Inserts at a density of 1.5×10^5 cells/cm^2. The cell membranes formed in the inserts (figure 2) were used for transport experiments 21 to 28 days postseeding. All cells had their growth medium changed every second day, and medium was always changed 24 hours before the transport experiments were performed.

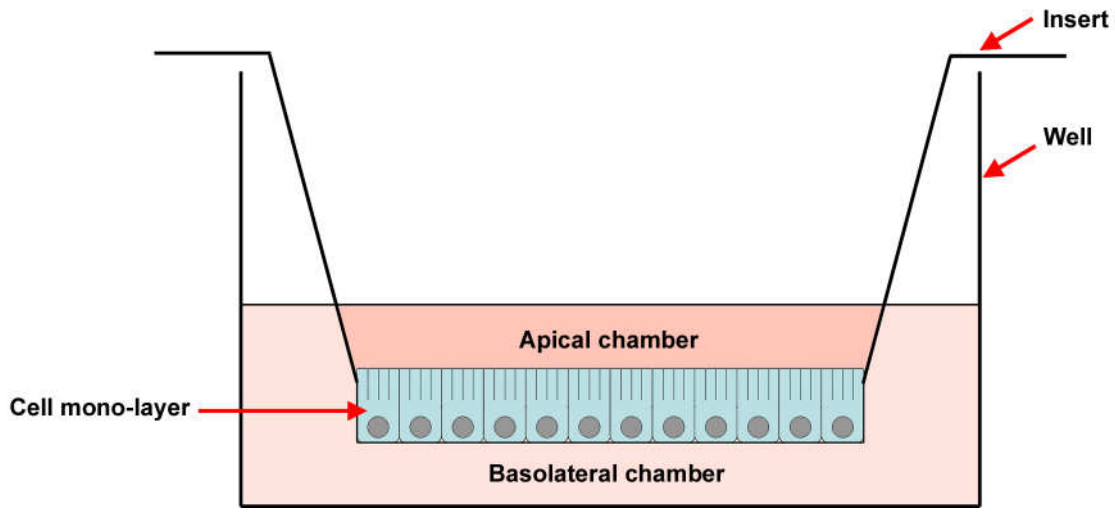

Figure 2. Schematic illustration of the Caco-2 membrane system used in paper I.

3.3.2 Cell Membrane Integrity

To ensure reliable P-gp transport data, the cell monolayer has to be tight without leakage between cells. The monolayer integrity was therefore monitored by measuring transepithelial electric resistance (TEER) and by measuring the transport of ^{14}C-mannitol.

The TEER is found by immersing electrodes in the basolateral and apical chambers, creating an electric circuit crossing the epithelial membrane. The electric resistance across the cell monolayer can thereby be measured. Potential leakage between cells would lower the electric resistance, and the TEER thus gives an indication of the tightness of the cell junctions. Wells with measured TEER values below the cut-off value of 150 $\Omega \cdot cm^2$ were not included in experiments.

Mannitol crosses the cell membrane only via the paracellular route, and the mannitol diffusion across a membrane with intact tight junctions should be low. Radiolabelled ^{14}C-mannitol was applied to the apical compartment, and the apical to basolateral transport was measured. None of the apparent permeability coefficients were greater than 1.0×10^{-6} cm/s, a limit suggested acceptable by others for adequate cell integrity[54].

3.3.3 P-gp Transport Experiments

Digoxin has been claimed to be a specific substrate for P-gp without significant affinity for other drug transporters[55], and digoxin has because of this become an established and recommended substrate for P-gp mediated transport experiments, and is often used as a P-gp reference substrate in the Caco-2 cell model[56].

Both the apical to basolateral (A-B) and basolateral to apical (B-A) transports were measured in the presence or absence of *E. purpurea*, St. John's wort and the positive inhibition control verapamil. Herbal extract or verapamil was always added to both the donor and to the receiver compartments in equal concentrations. Due to addition of herbal ethanol solutions, the concentration of 0.8% ethanol was kept equal through all

herbal and reference transport studies. The incubations were initiated by the addition of radiolabelled ^{3}H-digoxin to the donor side, and the cells were incubated with gentle vibration for 90 minutes. After incubation, 100µL aliquots from both donor and receiver compartments were transferred to scintillation vials for liquid scintillation counting.

3.4 Quantification Methods

3.4.1 Fluorometric Quantification

Fluorescence is the emission of electromagnetic radiation from a substance which recently has absorbed energy by excitation from other electromagnetic radiation. Usually, the emitted radiation has lower energy than the absorbed radiation, and thus a longer wavelength.

Some of the CYP3A4 metabolites have fluorescent qualities, and the metabolite quantities can thereby be estimated by measurement of fluorescence after incubations. The two CYP3A4 substrates BFC and BQ are metabolized to the fluorescent metabolites 7-hydroxytrifluoromethylcoumarin (HFC) and 7-hydroxyquinoline (HQ), respectively. With a microplate fluorometer, the emitted fluorescence was measured on excitation wavelength 410 nm and emission wavelength 538 nm. By comparison with fluorescence standard curves of known HFC and HQ concentrations, the amounts of metabolite generated in incubations were quantified.

With fluorometric assays there is a possibility of quantification error caused by self-fluorescence and quenching from the herbal constituents. This was corrected for in our studies.

3.4.2 High-Performance Liquid Chromatography (HPLC)

With high-performance liquid chromatography (HPLC), quantification of a wide range of molecules and drugs is made possible. The main purposes of the HPLC system are to separate and quantify constituents from a mixture. In short, suitable liquid solvents (so-called “mobile phase”) are pumped into the HPLC system at a fixed rate (and mixed, if required) by a pump (figure 3). An aliquot of the specimen is introduced into the mobile phase by the injector and carried to the column (“stationary phase”). The column contains small particles with a certain size, charge and surface characteristics. The different molecules in the injected solution are hindered differently by these particles due to the mass, shape, electrical charge etc. of the molecules, and will thereby exit the end of the column at different times. As an example, the hydrophobic molecules in the injected specimen will adhere stronger to a column’s hydrophobic particles and stay retained longer, while the sample’s hydrophilic molecules will have a low affinity to the column’s hydrophobic particles and thus be carried faster through the column by a hydrophilic mobile phase. Consequently, the separation depends on properties of both the mobile phase and the column.

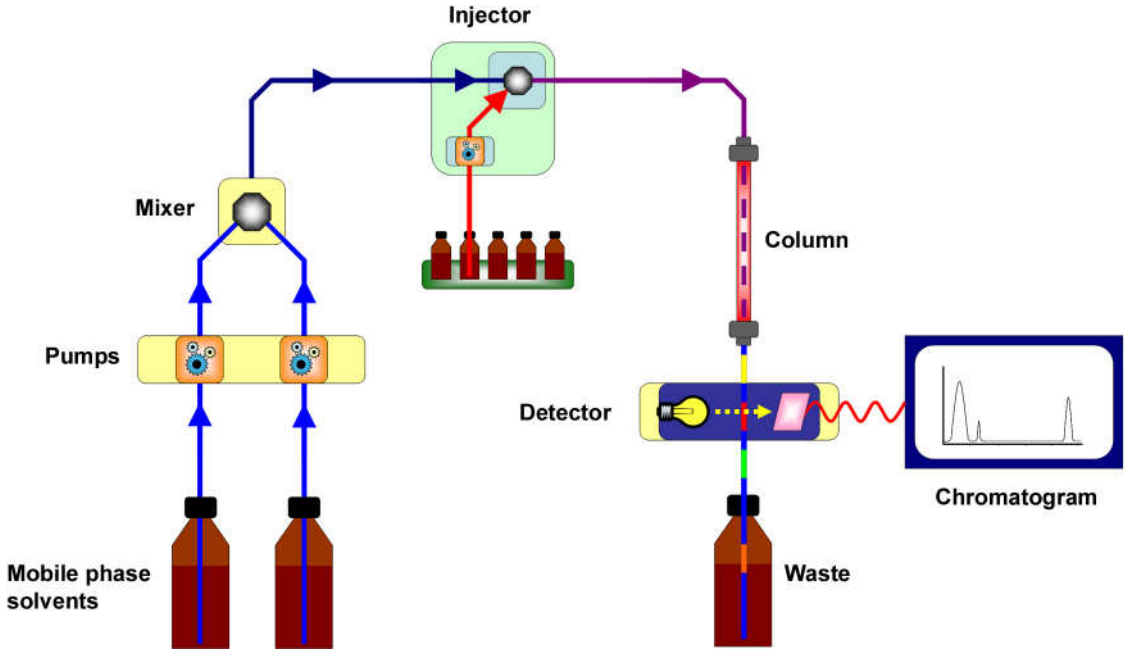

Figure 3. Schematic model of the HPLC system

After the substances from the injected solution are separated by this filtration, they are introduced to a detector device, set to measure key physiochemical properties of the target component(s) of the sample. The detectors response is measured over time and printed as a chromatogram. If well-defined separation of constituents has been achieved, each amplitude peak in the final chromatogram reflects one of the separated substances. The area and height of each peak can then be used to estimate the amount of each substance by comparison with standard curves of known concentrations of the substances. After passing the detector, the mobile phase with the previously injected sample is ejected as waste.

In our studies, HPLC was used for quantification of the CYP3A4 metabolite 6-β-OH-testosterone. The HPLC system included a Supelco LC18 column (150mm, ¼", 5µm) (paper II) or Zorbax Eclipse XDB-C18 column (4.6x150mm, 5µm) (paper III). The mobile phase was methanol:water with proportions selected on the basis of well-defined peak separation in the chromatogram. The metabolite 6-β-OH-testosterone was detected by ultraviolet (UV) light absorbance at 254 nm (paper II) or 240 nm (paper III) wavelength. The metabolite concentrations were estimated from the chromatogram peak areas by comparing with standard curves of known concentrations of pure 6-β-OH-testosterone. Quality controls with low, middle and high concentrations of 6-β-OH-testosterone were present in duplicate in all standard curves. For further details about the HPLC assays and materials, it is referred to paper II and III.

3.4.3 Liquid Scintillation Counting

Liquid scintillation counting is a standard technique for quantification of radioactivity, usually β-decays. Tritium (^{3}H) and carbon-14 (^{14}C), as used as radiolabels in our studies, undergo β-decay into helium-3 (^{3}He) and nitrogen-14 (^{14}N), respectively, emitting electrons with relatively low energy. Due to the radiation's low energy, these isotopes are less hazardous in laboratory use, but also more difficult to detect directly. With liquid scintillation counting, samples containing the radiolabelled target molecules

are dissolved in a scintillation cocktail containing organic solvent molecules and scintillator molecules. When β-emitted electrons interact with the solvent molecules, the electrons' energy is absorbed by the solvent molecules, which in turn transfer the energy to the scintillator molecules. The excited scintillator molecules then dissipate this energy by emitting a photon as electromagnetic radiation, and this pulse of light is possible to detect by the scintillation counter. Ideally, every emitted electron should by this reactive chain lead to one emitted photon, but usually there is a discrepancy between the nuclear disintegrations per minute (dpm) and the registered counts per minute (cpm). This discrepancy ratio (dpm/cpm) is called counting efficiency.

In our cell membrane transport studies, aliquots from donor and receiver compartments were dissolved in an Optiphase Supermix scintillation cocktail (PerkinElmer, USA) and counted for 10 minutes by a Beckman scintillation counter (Beckman Coulter, USA). Vials with known dpm and concentration of ^{3}H-digoxin and ^{14}C-mannitol were included to calculate counting efficiencies and to make concentration standard curves. Counting efficiencies were calculated to 26% for ^{3}H-digoxin and 95% for ^{14}C-mannitol. No quenching was observed.

3.5 Enzyme Activity and Pharmacokinetic Parameters

The basic CYP3A4 activity was expressed as the amount of metabolite formed per amount of CYP3A4 enzyme per minute (pmol metabolite × pmol enzyme^{-1} × min^{-1}). Transport through cell membranes in each direction was measured as the apparent permeability coefficient, P_{app} (cm/s). The net flux, J_{Net} (nmol/cm^2/h), express the net transport in B-A direction, i.e. the A-B transport subtracted from B-A directed transport.

Activity in presence of inhibitor was expressed as the percentage of the basic (control) activity without herb/inhibitor, but otherwise identical conditions. The IC_{50} values (inhibitor concentration resulting in a 50% inhibition of CYP3A4-mediated metabolism or net digoxin flux) were calculated from best-fit regression of inhibition plots. The maximum enzyme activity rate (V_{max}), the substrate concentration at which ½ × V_{max}

occurs (K_m) and modes of inhibition were determined from Lineweaver-Burk plots or Eadie-Hofstee plots.

3.6 Statistics

Results were mainly expressed as mean values ± standard deviation (SD) if not stated otherwise. Values of $p < 0.05$ and non-overlapping 95% confidence intervals were set *a priori* to be considered as statistically significant. Difference between groups was analyzed with two-sample Student's *t*-test. Confidence intervals (95%) were estimated for IC_{50} values in paper III.

Statistical analyses were performed with Microsoft Office Excel 2003 and SigmaPlot.
All data processing, graphs, regressions and statistical analyses were made with Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, USA) and SigmaPlot (version 10 and 11, Systat Software Inc., Richmond, USA).

4. Results and Discussion

4.1 Herbal Products

In the wide specter of herbal medicinal products, many of these are based on a "whole herbal extract". Such products include a complex mixture of different constituents with often unknown specific concentrations. Several investigations have been performed to identify the assumed medically active ingredients from different herbs. Isolated from St. John's wort, the components hypericin and hyperforin have shown to play significant roles in the therapeutic effects on depression and in the interactions with CYP3A4 and P-gp[12;57]. For Echinacea, a recent study has shown that specific alkylamide constituents contribute to the inhibitory effects on CYP3A4, however, the total inhibition of the whole herb extract could not be explained by these specific substances alone[58].

We chose to use whole herb extracts, as provided for sale to consumers, directly in our studies. Consequently, we also include more complex possible interferences by *E. purpurea* in our evaluation of interference, such as constituent–constituent interactions and allosteric, contributing or counteracting enzyme interactions from different herbal components, as possible to be present after ingestion of the whole-herb extract. When using a whole-herb extract, it is, however, difficult or impossible to assign the observed effects to specific herbal substances, or to interpret the number of active constituents involved. Furthermore, due to the high-grade variation observed for the chemical composition of different Echinacea preparations, it is difficult to directly compare the results with other Echinacea studies where other herbal preparations have been used[10]. It has been shown great variety in inhibition potential from different Echinacea products, tested with identical assays[58]. Hence, care needs to be taken when comparing results with other studies.

In our studies, we have tested two single-herbal *E. purpurea* products, Echinagard® (Madaus AG, Germany) and Echinaforce® (A. Vogel, Bioforce AG, Switzerland). These products are similar with respect to their ethanol extraction of mainly overground parts of *E. purpurea* plant. Their respective dry mass contents of *E. purpurea* plant and

their recommended clinical dosages are similar, however, not strictly identical. However, a study published concurrently with our work has shown a striking difference in the alkylamide quantities in these products, as the total alkylamide levels in Echinaforce® was ca. 60-fold of the levels in Echinagard®[58]. Large variation of phytochemical contents in Echinacea has been extensively described, depending e.g. on the plant parts used, the season of harvest, growth locations, plant developmental stages and preparation methodology[59-61]. Although seeming relatively analogous for both consumers and researchers, the specific preparations may thus be significantly divergent.

The range of herbal concentrations selected for these studies were based on estimations of clinically relevant levels after ingestion. The single and daily dosages in 1 liter of gastrointestinal or 56 liters of total body fluid were used as estimations of maximal clinical levels, in accordance with approaches used in earlier studies[51;62;63]. The concentration ranges used in the incubations were set to cover this maximal level and the lower herbal concentrations, and should thereby represent a probable range of physiologically and clinically relevant *E. purpurea* concentrations.

4.2 Effects of *E. purpurea* on CYP3A4

As described in paper II and III, we found a minor inhibitory potential of *E. purpurea* towards CYP3A4 mediated metabolism. Thus, our findings qualitatively support previous *in vitro* studies reporting inhibitory effects on CYP3A4 from *E. purpurea*[58;64-66]. The quantitative comparison between studies is complicated by several factors. Firstly, different terms are used for the inhibitory potential. To aid in the objective comparison, we chose to express the IC_{50} in absolute terms, as mg of dried herb per mL, rather than relative terms used by several others (e.g. % of full strength)[64;65]. Secondly, the specific herbal product tested may not be directly comparable with other products. Some of the studies on Echinacea inhibition are based on other Echinacea species, such as *E. angustifolia* or *E. pallida*, or multiherbal products which includes various herbs[67;68]. Significant variation in inhibitory potential has also been shown between the

different products of *E. purpurea*, corresponding to a factor of more than 140 between the most and least potent *E. purpurea* product, probably due to their considerable variation in phytochemical composition[10;58]. Thirdly, the inhibition varies due to the choice of CYP3A4 substrate, as reported in paper II and further discussed in section 4.5.6.

We reported mean IC_{50} levels for the CYP3A4 inhibition by *E. purpurea* ranging from 121.5 to 5394 µg/mL. This is in the same total range (from 12.7 to 5030 µg/mL) as reported by quantitatively comparable studies[58;66]. More specifically, a study by Hellum and Nilsen (2008), originating from the same laboratory as our research, reported an IC_{50} value of 5030 µg/mL for Echinagard® using testosterone/HPLC methodology, comparable to our IC_{50} value of 5394 µg/mL in paper II. Modarai *et al.* (2007) reported the IC_{50} for Echinagard® at 1812 µg/mL using the BFC/fluorescence methodology, regarded as reasonably corresponding to our measured IC_{50} at 354 µg/mL (paper II).

For the Echinaforce® product, no directly comparable reports using a similar testosterone/HPLC methodology have been found in the literature. However, Echinaforce® produced a significantly higher degree of inhibition than Echinagard®, when measured with the testosterone/HPLC methodology. This observation is supported by Modarai *et al*. (2007), reporting a similar difference in inhibitory potency for these specific products by using a BFC/fluorescence methodology[58].

The *in vivo* studies on the effects of *E. purpurea* on CYP3A4 mediated metabolism are divergent. Gorski *et al*. (2004) reported that *E. purpurea* produced inhibitory effects on intestinal CYP3A4, while inducing the hepatic CYP3A4 activity[69]. Gurley *et al*. (2004) found only minor effects of *E. purpurea* on the CYP3A4 mediated metabolism of midazolam[70]. Penzak *et al*. (2010) reported reduced exposure and increased clearance of midazolam, suggesting a total inducing effect on CYP3A4[71]. Although *in vitro* studies indicate an inhibitory potential of *E. purpurea* on CYP3A4 mediated metabolism, the effects *in vivo* are still more uncertain.

The *E. purpurea* inhibition pattern was in paper III consistent with a mechanism-based inhibition of CYP3A4, which to our knowledge was not previously published in the

literature. This finding could be of clinical interest, because mechanism-based inhibitors act irreversibly with consequently prolonged effects. Even smaller doses of *E. purpurea* could theoretically block CYP3A4 enzymes, and if additive herbal delivery and blocking of CYP3A4 exceed the rate of enzyme re-synthesis, repeated herbal delivery might increase the CYP3A4 inhibition even with smaller herbal dosages. This is, however, theoretical reflections which have not been documented for *E. purpurea* in *in vivo* studies.

Further pharmacokinetic analyses indicate heterotropic positive cooperative effects caused by the interaction by one or more *E. purpurea* constituents. The clinical implications of this are far from known, but at least in theory, such effects could imply that the possible inhibition caused by *E. purpurea* weakens when the concentration of the interactive CYP3A4 substrate rises.

4.3 P-glycoprotein Inhibition

In paper I, possible inhibition by *E. purpurea* towards P-glycoprotein drug transport was evaluated. P-gp is a widely studied drug efflux transporter[72;73], and it has caught much attention because of its ability to modulate the absorption and distribution of drugs in the human body[43;74].

In the *E. purpurea* concentrations above 0.4 mg/mL, a linear dose-related inhibition of the net digoxin flux was observed, with a 22.3% decreased net digoxin flux at 6.36 mg/mL *E. purpurea* concentration, but the statistically significant linear correlation indicates that further inhibition may occur at higher *E. purpurea* concentrations. We did not measure a 50% inhibition of P-gp transport in presence of *E. purpurea*, indicating that the IC_{50} of *E. purpurea* on P-gp inhibition is higher than 6.36 mg/mL. However, a P-gp inhibition in order of 22.3% should still be sufficient to cause a reduced active secretion of digoxin, and increase the absorption of P-gp drug substrates. With reference to reports from the P-gp inhibitor atorvastatin, it is indicated that a notable clinical effect may occur at intestinal drug concentrations below the IC_{50} for P-gp inhibition[75;76].

In paper I, we observed an increase in the net digoxin flux in lower *E. purpurea* concentrations. Again, the complex composition of "whole herbal extracts" can, at least in theory, explain this dual effect. Results from green tea studies show that some green tea catechins cause inhibitory effects on P-gp activity in Caco-2 cells[77], while other green tea catechins enhance the P-gp mediated transport in the NIH3T3-G185 cell line, with indications of an allosteric site activation as the mechanism[78]. It is possible that different chemical constituents in the extract from the total *E. purpurea* herbal product exert different effects; the allosteric activating constituent(s) being the dominating at lower concentrations and the inhibiting constituent(s) the dominating at higher concentrations. In our experiments evaluating the inhibition pattern of *E. purpurea*, we found that *E. purpurea* (1.6 mg/mL) decreased both V_{max} and K_m, compatible with an uncompetitive inhibition of the P-gp transport mechanism, thus indicating a complex nature.

Our experiments for the evaluation of P-gp inhibition by *E. purpuea* were performed with the marketed product Echinagard®, which in CYP3A4 studies has shown significantly lower alkylamide levels and CYP3A4 inhibition compared to other and similar marketed products[58]. Whether a similar product dependency exists for the inhibition of P-gp, is unknown in the current literature. Stronger P-gp inhibition by *E. purpurea* might thus exist, but remains as speculations, and needs to be evaluated in further studies.

One study in the current literature has evaluated the *in vivo* effects by Echinacea on P-gp. Intake of a combined preparation containing *E. purpurea* and *E. angustifolia* was found not to influence the venous digoxin disposition after a single oral digoxin administration, indicating that Echinacea is not a potent modulator of P-gp *in vivo*[79]. However, general clinical conclusions may not be drawn from this study alone, as effects on steady-state kinetics, clinically relevant drug levels, various P-gp substrates and various Echinacea preparations are among the factors which are still not evaluated *in vivo* in the published literature.

4.4 Sambucus Force and CYP3A4

Sambucus Force is a multiherbal product consisting of 46% dried *Sambucus nigra* extract, 46% dried *Echinacea purpurea* (aerial part), 5% dried Royal Jelly and 3% dried *Olea europaea* extract. To our knowledge, no data on Sambucus Force's ability to interact with CYP3A4 has previously been published. Sambucus force was found to inhibit the CYP3A4 activity with an IC_{50} value of 1192µg/mL, and with reference to other herbal inhibitors, Sambucus Force is considered as a relatively weak inhibitor of CYP3A4[66;80].

For the comparison between the multiherbal and single-herbal products, the corresponding amounts of *E. purpurea* raw-plant material to that of the dried constituents in Sambucus Force and Echinaforce®, were calculated for each of the IC_{50} values. Expressed as IC_{50} equivalents of *E. purpurea* in each product, no significant difference was found, and, thus, it seems that *E. purpurea* alone accounts for the total CYP3A4 inhibition that is exerted by Sambucus Force. This further implicates that the other herbal components, including *Sambucus nigra*, seem to possess an insignificant inhibition potential towards CYP3A4.

Interestingly, the multiherbal and single-herbal products exerted different inhibitory mechanisms. Sambucus Force produced a time-dependent, but not NADPH-dependent, inhibition. Hence, the criteria for mechanism-based inhibition were not fulfilled. The inhibition pattern for Sambucus Force was further found to be compatible with uncompetitive inhibition mechanisms. However, as described in paper III, a substrate-dependent uncompetitive inhibition has to be different from the time-dependent inhibition observed in absence of substrate. Thus, at least two different inhibitory mechanisms were observed. Multiple CYP3A4 inhibition mechanisms have been reported previously, such as for grapefruit juice, where bergamottin (BG) and 6'7'-dihydroxybergamottin (DBG) are the most abundant furanocoumarin contents. DBG has shown reversible substrate-*independent* inhibition, whereas BG is a substrate-*dependent* reversible inhibitor[81]. Furthermore, these two compounds differ in times of onset of intestinal CYP3A4 inhibition, where DBG acts rapidly and exerts its maximal

inhibition before BG starts to act[82]. A recent study on *Aloe vera* reported a dual, time-dependent inhibition, suggested to arise from different chemical components in *Aloe vera* juice[83].

Our studies do not provide an evident explanation for the observed differences in inhibitory mechanism of *E. purpurea* in the multiherbal and single-herbal product. However, as further described in paper III, such differences may arise from interferences of effects by the constituents in the preparations, or herb-herb interactions arising in the multiherbal product, as previously suggested for other herbal preparations such as *Orthosiphon stamineus* and for Aconitum and Glycyrrhiza[84;85].

4.5 Methodological Considerations

4.5.1 Herbal Preparations

In the work with herbal remedies, there are some challenges needed to be addressed. The chemical composition of herbal remedies is often unknown, in contrast to regular pharmaceutical research on known molecular substances. In our studies, the herbal preparations were given thorough considerations. Where labeling of the herbal products was considered inadequate, inquiries for further information were made to the manufacturers. The dry capsular products were extracted according to pre-defined extraction procedures, and both ethanol solutions and purified water were used as solvents. To enable proper concentration measurement and comparison, all extracts were dried before used, and the dried extract weight was used as basis for all herbal concentrations. Herbal working solutions were, as all other chemicals, stored according to pre-defined temperatures, sunlight shielding, shelf-life etc. However, some differences between the experimentally prepared *E. purpurea* products were inevitable, as further detailed in the respective papers I-III.

4.5.2 Effects of Ethanol

In paper I and II, an ethanol solution of *E. purpurea* was used. When preserving the original herbal composition and keeping ethanol concentrations below 0.8%, the maximum concentration of *E. purpurea* possible to reach in incubations was 6.36 mg/mL. A more precise estimate of *E. purpurea*'s IC_{50} on P-gp in paper II could have been possible if higher herbal concentrations were used in the studies, but this would cause elevated ethanol concentrations, and the herbal concentrations would be above the estimated clinical concentration range. Partly due to these limitations caused by the ethanol, *E. purpurea* was in the assays for paper III redissolved in purified water only.

Ethanol concentrations were kept constant at set levels, and all respective control solutions had equal ethanol contents as the herbal solutions. All presented pharmacokinetic inhibition values were corrected for the possibly inhibitory effects of the ethanol present.

In paper I, we found that 0.8% ethanol, the level caused by addition of herbal ethanol extracts, significantly decreased the net digoxin flux through Caco-2 cells. As concentrations of ethanol around 0.8% previously have been shown to have no or negligible effect on Caco-2 cell viability[86;87], this was certainly unexpected. It was concluded that the effects are in concordance with an inhibitory effect of low ethanol levels on P-gp, which to our knowledge have not been described previously in the literature. This arise a question whether moderate drinking could affect P-gp mediated drug pharmacokinetics in clinical cases.

4.5.3 Caco-2 Cell System

The Caco-2 cell line express P-gp when they are cultured to make a monolayer, as previously described in section 3.3.1, and this cell line has served as a preferred method for permeability screening by the pharmaceutical industries. However, the relevance of the results obtained *in vitro* can be difficult to assess and extrapolate to *in vivo*

situations, because P-gp only represents a limited part of the *in vivo* systems for metabolism and distribution of drugs.

To ensure reproducibility, a narrow set of passages were seeded for monolayer generation. Experiments were performed during the fixed interval of 21 and 28 days post-seeding, when the monolayer cells are confluent and the P-gp expression is at a peak[88;89].

We chose to use the P-gp substrate digoxin as it has been claimed to be a specific substrate for P-gp[55]. More recently, studies have indicated that organic anion transporting polypeptides (OATP) may also play a role in P-gp transport[90]. However, digoxin is still an established and recommended substrate for P-gp mediated transport experiments[56;91], and is often used as a P-gp reference substrate in the Caco-2 cell model.

In paper I, we found that verapamil (100µM), an established potent inhibitor of P-gp mediated transport, did not cause a total P-gp inhibition. Other studies have reported total inhibition of P-gp activity by verapamil, even at lower concentrations (20µM), with a ratio between B-A and A-B directed transport ($R_{B\text{-}A/A\text{-}B}$) close to 1.0 [54;92]. Our $R_{B\text{-}A/A\text{-}B}$ at 1.45 is not fully consistent with these findings, and we have no obvious explanation for this discrepancy. However, a $R_{B\text{-}A/A\text{-}B}$ of 1.29 with 100µM verapamil was reported in one study similar to our[93]. Using vinblastine as a P-gp substrate, substrate flux values equivalent to a $R_{B\text{-}A/A\text{-}B}$ of 2.08 has also been shown[74], and even at a verapamil concentration as high as 500µM, a ratio of 3.6 has been reported for transport of saquinavir[94]. Our data therefore indicate, as have also been indicated by other investigations, that verapamil (100µM) is not a 100% inhibitor of P-gp transport.

4.5.4 CYP3A4 Metabolism

Isolated human CYP enzymes are now commercially available, enabling *in vitro* studies on single CYP subtypes without the influence of other systems. Isolated CYP enzymes

may be expressed in bacteria (such as *Escherichia coli*), yeasts, insect cells or mammalian cells[95]. In paper II and III, the CYP3A4 enzyme was produced from insect cells infected with baculovirus expressing the recombinant human cDNA for CYP3A4. It is debatable whether enzymes produced by insect cells are representative for the enzymes located in e.g. the human liver cells *in vivo*. Studies have, however, suggested that recombinant cDNA supersomes were just as suited for predicitive metabolism studies as if using human liver microsomes[95]. In the attempts for extrapolation from *in vitro* results to *in vivo* relevance, it is further important to be aware the potential differences in enzyme concentrations, and the presence of necessary cofactors, between the *in vitro* and *in vivo* systems.

4.5.5 Quantification of Metabolites

The high-throughput fluorometric assay for evaluation of CYP3A4 inhibition potential is dominating as method for evaluation of *E. purpurea*, and the majority of the *in vitro* CYP3A4 studies published on *E. purpurea* are based on fluorometric quantification of metabolites[58;64;65;67]. With this methodology, the incubations are performed in 96-well microtiter plates, and the quantification is quickly performed by fluorometric measurements. When investigating "whole herbal extracts", several herbal constituents are present in the incubations, and there is a certain possibility of quenching and self-fluorescense from these constituents. If not corrected for, this may interfere with the fluorometric measurements, as reported for the *E. purpurea* experiments by Yale and Glurich (2005)[65]. By correcting for intrinsic fluorescense and quenching properties, we sought to reduce the source of error.

The HPLC measurement technology is also based on standardized procedures, but is both more expensive due to the need for higher incubation volumes and more time consuming due to the filtration process. In order to obtain good quantification reproducibility, validated methodologies should be strictly followed[96].

4.5.6 Choice of CYP3A4 Substrate

The substrate-dependency of CYP3A4 drug inhibitory profiles is well known. This is previously shown for ketoconazole, where the IC_{50} of ketoconazole varied by a factor of 180 when evaluated with testosterone and BFC[97]. For cyclosporine, the corresponding factor was more than 500 in a similar study[98]. However, for herbal medicines, the substrate-dependency of CYP3A4 is far less evaluated. We chose to include ketoconazole and St. John's wort for comparison with *E. purpurea* when investigating the substrates' influence on inhibition profiles.

In paper II, we found that the inhibition by *E. purpurea* on CYP3A4 metabolism of testosterone, was less potent compared to the inhibition of BFC and BQ metabolism. Whether this is due to differences between HPLC and fluorescent quantification techniques or due to different inhibition mechanisms, can not be concluded from our studies. However, previous studies on *E. purpurea* with fluorescent metabolites have shown a mild CYP3A4 inhibition measured with BFC, while a mild activation was measured with low concentrations of the substrate benzyl ether resorufin (BzRes)[65]. This supports that the substrates may be differently inhibited by *E. purpurea*.

The composition of "whole herbal extracts" is complex, and the CYP3A4 binding sites of the *E. purpurea* active constituents are to our knowledge not known. It is, however, suggested previously that testosterone, BFC and BQ bind to different domains in the CYP3A4[99]. Knowledge about binding sites is certainly a key to the understanding of CYP inhibition patterns from herbs and drugs and selection of appropriate substrates. Our results, and other reports of substrate-dependent inhibition, complicate the interpretation and evaluation of CYP3A4 inhibitory potential, and the choice of substrates used for such evaluation should be given adequate attention. However, despite the high variations in CYP3A4 substrate metabolism reported earlier, we found reasonably conformity between all substrates when measuring the interaction potential of St. John's wort and ketoconazole. Somewhat contrary to the varying results from *E.*

purpurea's inhibitory potential, such conformity supports the use of these substrates for evaluation of CYP3A4 inhibition.

4.6 Clinical Relevance

As discussed above, the complex chemical composition of a "whole herbal extract" may be the source for methodical difficulties, complex interactions patterns and even methodical error. However, when preserving the original composition of the extract, we evaluate the same extract as actually ingested by the patients. The complexity observed both by substrate-dependent CYP3A4 inhibition and by dual concentration-dependent effects on P-gp interaction, reflects the possible complexity *in vivo* caused by ingestion of such herbal extracts.

Extrapolations from *in vitro* studies to the clinical relevance *in vivo* must be performed with great care. Numerous factors play roles in the complex systems of the human body. In pharmacokinetic terms, there are factors such as intestinal uptake, serum protein binding, drug disposition due to transporter proteins, enzyme degradation by metabolism, and liver or kidney excretion, all of which are working simultaneously *in vivo*. Isolated systems as evaluated *in vitro* may thus at best give indications for the clinical outcomes.

Our studies on *E. purpurea* generally indicate a relatively low *in vitro* inhibition potential towards CYP3A4 and P-gp activities. In the prediction of *in vivo* relevance, the dosages must be taken into account, and the IC_{50} values in study III were therefore mathematically adjusted for the recommended dosages. The single-herbal product was thus considered unlikely to reach IC_{50} levels when administered in recommended dosages, but for the high-dosed multiherbal product, possible *in vivo* effects can not be excluded.

Despite the extensive use of *E. purpurea* in the population, and the potentially hazardous herb-drug interactions discovered for other herbs, the knowledge about CYP3A4 interactions with *E. purpurea* is still limited. Generally, *in vitro* studies report

inhibitory effects of *E. purpurea* on CYP3A4 metabolism[58;64;65;67], and further supported in our studies. However, the effects observed *in vivo* are varying, and both inhibition and induction has been reported[69-71]. Recent reviews suggest that Echinacea is unlikely to pose serious health threats due to drug pharmacokinetic interactions, although more research is claimed to be needed[16;100].

It is of notable clinical interest that *E. purpurea* seems to be a mechanism-based inhibitor of CYP3A4. The irreversible nature of this inhibition may in theory result in an increasing clinical inhibition with regular use of smaller doses. Grapefruit juice, in which several components have shown to be mechanism-based CYP3A4 inhibitors, is well known for its ability to cause clinically relevant interactions due to CYP3A4 inhibition[14;101]. Thus, further *in vivo* studies with *E. purpurea* should seek to evaluate possible clinical effects due to irreversible inhibition mechanisms.

The substrate-depending effects of *E. purpurea* on CYP3A4 metabolism found in our studies, complicates the interpretation of *E. purpurea's* clinical interaction potential. In order to find a more general inhibition potential of *E. purpurea* on CYP3A4, if possible, several CYP3A4 substrates should be evaluated. It is noteworthy that all published studies on *E. purpurea*'s effects on CYP3A4 *in vivo*, are performed using midazolam as probe substrate[69-71]. Thus, substrate-dependent effects have not been evaluated in clinical studies. Possible substrate-dependency of CYP3A4 *in vivo* should also be taken in account in the evaluation of *E. purpurea's* clinical interaction potential.

Several of the P-gp substrates are also substrates for CYP3A4[54;73;102], and there is a significant co-localisation of CYP3A4 and P-gp in the enterocytes[44]. Synergistic P-gp/CYP3A4 effects may occur as increased P-gp-mediated efflux would return the oral drug to the extracellular intestinal lumen after uptake in a repeated circulation, and thus prolong the time the P-gp/CYP3A4 substrate can be subject to metabolism by intestinal CYP3A4[54]. The alterations of CYP3A4 activity by *E. purpurea* might therefore add on to the effects on P-gp reported in our studies in the same way as those synergistic CYP3A4/P-gp effects earlier reported for cyclosporine[103] and the black pepper consituent piperine[104], and the combined effects *in vivo* can be more extensive than

those individual effects reported on P-gp and CYP3A4 *in vitro*. Such combined effects of *E. purpurea* on P-gp and CYP3A4 may, at least in theory, be clinically relevant, especially for drug bioavailability, and should therefore be subject to further studies. Furthermore, possible effects of *E. purpurea* on other CYP isoenzymes, transporter enzymes, protein binding or other mechanisms involved in absorption, distribution, metabolism and excretion of drugs, should also be taken in account when evaluating the total implications of *E. purpurea*'s pharmacokinetic interactions.

5. Conclusions

This thesis brings more knowledge about the interaction potential for *E. purpurea* towards CYP3A4 and P-gp *in vitro*. Based on the addressed questions, the following conclusions are drawn:

- Does *E. purpurea* inhibit P-glycoprotein mediated efflux transport *in vitro*?
    - Yes, *E. purpurea* seems to be a relatively weak inhibitor of P-gp-mediated transport of digoxin *in vitro*
- Does *E. purpurea* inhibit CYP3A4 mediated metabolism *in vitro*?
    - Yes, *E. purpurea* seems to possess a relatively low inhibition potential towards CYP3A4 activities *in vitro*.
- Does the choice of substrate and experimental methodology influence on the inhibition patterns of *E. purpurea* on CYP3A4?
    - Yes, the observed inhibitory potential and mechanisms of inhibition was dependent on the substrate and/or methodology used in the laboratory experiments.
- What type of inhibition is exerted on CYP3A4 by *E. purpurea*?
    - As a single-herbal preparation, *E. purpurea* seems to exert heterotropic cooperative binding effects on CYP3A4. This further implicates that the measured CYP3A4 inhibitory levels are varying with the substrate concentrations.
- Is *E. purpurea* a mechanism-based inhibitor of CYP3A4?
    - *E. purpurea* show both time- and NADPH-dependent pre-incubation inhibition, which is consistent with mechanism-based inhibition.
- What is the inhibitory contribution of *E. purpurea* towards CYP3A4 when being part of a multiherbal preparation?
    - The inhibition from the multiherbal product Sambucus force seemed in strength to be exclusively exerted by its *E. purpurea* constituents. However, the inhibitory pattern was uncompetitive, and nonconforming with mechanism-based inhibition. These divergences from the single-

herbal product are suggested to be caused by herb-herb interactions or stabilization processes in the multiherbal product.

- Do our *in vitro* data indicate that *E. purpurea* represents a significant risk for pharmacokinetic drug interactions *in vivo*?
    - The inhibitory potential of *E. purpurea* was relatively weak *in vitro* towards both CYP3A4 and P-gp, and clinical effects thus might seem relatively unlikely. However, our findings of irreversible inhibition of CYP3A4 can not rule out possibilities for clinical relevant effects of *E. purpurea* on the pharmacokinetics of drug CYP3A4 substrates *in vivo*. These matters should be evaluated by long term administrations of both *E. purpurea* and different CYP3A4 substrates in man.

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Echinacea purpurea and P-Glycoprotein Drug Transport in Caco-2 Cells.

Torstein Schrøder Hansen and Odd Georg Nilsen

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In vitro Inhibition of CYP3A4 by the Multiherbal Commercial Product Sambucus Force and its Main Constituents *Echinacea purpurea* and *Sambucus nigra*.

Torstein Schrøder-Aasen, Guri Molden and Odd Georg Nilsen

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164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR

189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

2002

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS

215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

2004

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY

240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

2005

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION

268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY

292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

2007

298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL
314. Erik Solligård: GUT LUMINAL MICRODIALYSIS
315. Elin Tollefsen: RESPIRATORY SYMPTOMS IN A COMPREHENSIVE POPULATION BASED STUDY AMONG ADOLESCENTS 13-19 YEARS. YOUNG-HUNT 1995-97 AND 2000-01; THE NORD-TRØNDELAG HEALTH STUDIES (HUNT)
316. Anne-Tove Brenne: GROWTH REGULATION OF MYELOMA CELLS

317. Heidi Knobel: FATIGUE IN CANCER TREATMENT – ASSESSMENT, COURSE AND ETIOLOGY
318. Torbjørn Dahl: CAROTID ARTERY STENOSIS. DIAGNOSTIC AND THERAPEUTIC ASPECTS
319. Inge-Andre Rasmussen jr.: FUNCTIONAL AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN NEUROSURGICAL PATIENTS
320. Grete Helen Bratberg: PUBERTAL TIMING – ANTECEDENT TO RISK OR RESILIENCE ? EPIDEMIOLOGICAL STUDIES ON GROWTH, MATURATION AND HEALTH RISK BEHAVIOURS; THE YOUNG HUNT STUDY, NORD-TRØNDELAG, NORWAY
321. Sveinung Sørhaug: THE PULMONARY NEUROENDOCRINE SYSTEM. PHYSIOLOGICAL, PATHOLOGICAL AND TUMOURIGENIC ASPECTS
322. Olav Sande Eftedal: ULTRASONIC DETECTION OF DECOMPRESSION INDUCED VASCULAR MICROBUBBLES
323. Rune Bang Leistad: PAIN, AUTONOMIC ACTIVATION AND MUSCULAR ACTIVITY RELATED TO EXPERIMENTALLY-INDUCED COGNITIVE STRESS IN HEADACHE PATIENTS
324. Svein Brekke: TECHNIQUES FOR ENHANCEMENT OF TEMPORAL RESOLUTION IN THREE-DIMENSIONAL ECHOCARDIOGRAPHY
325. Kristian Bernhard Nilsen: AUTONOMIC ACTIVATION AND MUSCLE ACTIVITY IN RELATION TO MUSCULOSKELETAL PAIN
326. Anne Irene Hagen: HEREDITARY BREAST CANCER IN NORWAY. DETECTION AND PROGNOSIS OF BREAST CANCER IN FAMILIES WITH *BRCA1*GENE MUTATION
327. Ingebjørg S. Juel : INTESTINAL INJURY AND RECOVERY AFTER ISCHEMIA. AN EXPERIMENTAL STUDY ON RESTITUTION OF THE SURFACE EPITHELIUM, INTESTINAL PERMEABILITY, AND RELEASE OF BIOMARKERS FROM THE MUCOSA
328. Runa Heimstad: POST-TERM PREGNANCY
329. Jan Egil Afset: ROLE OF ENTEROPATHOGENIC *ESCHERICHIA COLI* IN CHILDHOOD DIARRHOEA IN NORWAY
330. Bent Håvard Hellum: *IN VITRO* INTERACTIONS BETWEEN MEDICINAL DRUGS AND HERBS ON CYTOCHROME P-450 METABOLISM AND P-GLYCOPROTEIN TRANSPORT
331. Morten André Høydal: CARDIAC DYSFUNCTION AND MAXIMAL OXYGEN UPTAKE MYOCARDIAL ADAPTATION TO ENDURANCE TRAINING

2008

332. Andreas Møllerløkken: REDUCTION OF VASCULAR BUBBLES: METHODS TO PREVENT THE ADVERSE EFFECTS OF DECOMPRESSION
333. Anne Hege Aamodt: COMORBIDITY OF HEADACHE AND MIGRAINE IN THE NORD-TRØNDELAG HEALTH STUDY 1995-97
334. Brage Høyem Amundsen: MYOCARDIAL FUNCTION QUANTIFIED BY SPECKLE TRACKING AND TISSUE DOPPLER ECHOCARDIOGRAPHY – VALIDATION AND APPLICATION IN EXERCISE TESTING AND TRAINING
335. Inger Anne Næss: INCIDENCE, MORTALITY AND RISK FACTORS OF FIRST VENOUS THROMBOSIS IN A GENERAL POPULATION. RESULTS FROM THE SECOND NORD-TRØNDELAG HEALTH STUDY (HUNT2)
336. Vegard Bugten: EFFECTS OF POSTOPERATIVE MEASURES AFTER FUNCTIONAL ENDOSCOPIC SINUS SURGERY
337. Morten Bruvold: MANGANESE AND WATER IN CARDIAC MAGNETIC RESONANCE IMAGING
338. Miroslav Fris: THE EFFECT OF SINGLE AND REPEATED ULTRAVIOLET RADIATION ON THE ANTERIOR SEGMENT OF THE RABBIT EYE
339. Svein Arne Aase: METHODS FOR IMPROVING QUALITY AND EFFICIENCY IN QUANTITATIVE ECHOCARDIOGRAPHY – ASPECTS OF USING HIGH FRAME RATE
340. Roger Almvik: ASSESSING THE RISK OF VIOLENCE: DEVELOPMENT AND VALIDATION OF THE BRØSET VIOLENCE CHECKLIST
341. Ottar Sundheim: STRUCTURE-FUNCTION ANALYSIS OF HUMAN ENZYMES INITIATING NUCLEOBASE REPAIR IN DNA AND RNA

342. Anne Mari Undheim: SHORT AND LONG-TERM OUTCOME OF EMOTIONAL AND BEHAVIOURAL PROBLEMS IN YOUNG ADOLESCENTS WITH AND WITHOUT READING DIFFICULTIES
343. Helge Garåsen: THE TRONDHEIM MODEL. IMPROVING THE PROFESSIONAL COMMUNICATION BETWEEN THE VARIOUS LEVELS OF HEALTH CARE SERVICES AND IMPLEMENTATION OF INTERMEDIATE CARE AT A COMMUNITY HOSPITAL COULD PROVIDE BETTER CARE FOR OLDER PATIENTS. SHORT AND LONG TERM EFFECTS
344. Olav A. Foss: "THE ROTATION RATIOS METHOD". A METHOD TO DESCRIBE ALTERED SPATIAL ORIENTATION IN SEQUENTIAL RADIOGRAPHS FROM ONE PELVIS
345. Bjørn Olav Åsvold: THYROID FUNCTION AND CARDIOVASCULAR HEALTH
346. Torun Margareta Melø: NEURONAL GLIAL INTERACTIONS IN EPILEPSY
347. Irina Poliakova Eide: FETAL GROWTH RESTRICTION AND PRE-ECLAMPSIA: SOME CHARACTERISTICS OF FETO-MATERNAL INTERACTIONS IN DECIDUA BASALIS
348. Torunn Askim: RECOVERY AFTER STROKE. ASSESSMENT AND TREATMENT; WITH FOCUS ON MOTOR FUNCTION
349. Ann Elisabeth Åsberg: NEUTROPHIL ACTIVATION IN A ROLLER PUMP MODEL OF CARDIOPULMONARY BYPASS. INFLUENCE ON BIOMATERIAL, PLATELETS AND COMPLEMENT
350. Lars Hagen: REGULATION OF DNA BASE EXCISION REPAIR BY PROTEIN INTERACTIONS AND POST TRANSLATIONAL MODIFICATIONS
351. Sigrun Beate Kjøtrød: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN ASSISTED REPRODUCTION
352. Steven Keita Nishiyama: PERSPECTIVES ON LIMB-VASCULAR HETEROGENEITY: IMPLICATIONS FOR HUMAN AGING, SEX, AND EXERCISE
353. Sven Peter Näsholm: ULTRASOUND BEAMS FOR ENHANCED IMAGE QUALITY
354. Jon Ståle Ritland: PRIMARY OPEN-ANGLE GLAUCOMA & EXFOLIATIVE GLAUCOMA. SURVIVAL, COMORBIDITY AND GENETICS
355. Sigrid Botne Sando: ALZHEIMER'S DISEASE IN CENTRAL NORWAY. GENETIC AND EDUCATIONAL ASPECTS
356. Parvinder Kaur: CELLULAR AND MOLECULAR MECHANISMS BEHIND METHYLMERCURY-INDUCED NEUROTOXICITY
357. Ismail Cüneyt Güzey: DOPAMINE AND SEROTONIN RECEPTOR AND TRANSPORTER GENE POLYMORPHISMS AND EXTRAPYRAMIDAL SYMPTOMS. STUDIES IN PARKINSON'S DISEASE AND IN PATIENTS TREATED WITH ANTIPSYCHOTIC OR ANTIDEPRESSANT DRUGS
358. Brit Dybdahl: EXTRA-CELLULAR INDUCIBLE HEAT-SHOCK PROTEIN 70 (Hsp70) – A ROLE IN THE INFLAMMATORY RESPONSE ?
359. Kristoffer Haugarvoll: IDENTIFYING GENETIC CAUSES OF PARKINSON'S DISEASE IN NORWAY
360. Nadra Nilsen: TOLL-LIKE RECEPTOR 2 –EXPRESSION, REGULATION AND SIGNALING
361. Johan Håkon Bjørngaard: PATIENT SATISFACTION WITH OUTPATIENT MENTAL HEALTH SERVICES – THE INFLUENCE OF ORGANIZATIONAL FACTORS.
362. Kjetil Høydal : EFFECTS OF HIGH INTENSITY AEROBIC TRAINING IN HEALTHY SUBJECTS AND CORONARY ARTERY DISEASE PATIENTS; THE IMPORTANCE OF INTENSITY,, DURATION AND FREQUENCY OF TRAINING.
363. Trine Karlsen: TRAINING IS MEDICINE: ENDURANCE AND STRENGTH TRAINING IN CORONARY ARTERY DISEASE AND HEALTH.
364. Marte Thuen: MANGANASE-ENHANCED AND DIFFUSION TENSOR MR IMAGING OF THE NORMAL, INJURED AND REGENERATING RAT VISUAL PATHWAY
365. Cathrine Broberg Vågbø: DIRECT REPAIR OF ALKYLATION DAMAGE IN DNA AND RNA BY 2-OXOGLUTARATE- AND IRON-DEPENDENT DIOXYGENASES
366. Arnt Erik Tjønna: AEROBIC EXERCISE AND CARDIOVASCULAR RISK FACTORS IN OVERWEIGHT AND OBESE ADOLESCENTS AND ADULTS
367. Marianne W. Furnes: FEEDING BEHAVIOR AND BODY WEIGHT DEVELOPMENT: LESSONS FROM RATS

368. Lene N. Johannessen: FUNGAL PRODUCTS AND INFLAMMATORY RESPONSES IN HUMAN MONOCYTES AND EPITHELIAL CELLS
369. Anja Bye: GENE EXPRESSION PROFILING OF *INHERITED* AND *ACQUIRED* MAXIMAL OXYGEN UPTAKE – RELATIONS TO THE METABOLIC SYNDROME.
370. Oluf Dimitri Røe: MALIGNANT MESOTHELIOMA: VIRUS, BIOMARKERS AND GENES. A TRANSLATIONAL APPROACH
371. Ane Cecilie Dale: DIABETES MELLITUS AND FATAL ISCHEMIC HEART DISEASE. ANALYSES FROM THE HUNT1 AND 2 STUDIES
372. Jacob Christian Hølen: PAIN ASSESSMENT IN PALLIATIVE CARE: VALIDATION OF METHODS FOR SELF-REPORT AND BEHAVIOURAL ASSESSMENT
373. Erming Tian: THE GENETIC IMPACTS IN THE ONCOGENESIS OF MULTIPLE MYELOMA
374. Ole Bosnes: KLINISK UTPRØVING AV NORSKE VERSJONER AV NOEN SENTRALE TESTER PÅ KOGNITIV FUNKSJON
375. Ola M. Rygh: 3D ULTRASOUND BASED NEURONAVIGATION IN NEUROSURGERY. A CLINICAL EVALUATION
376. Astrid Kamilla Stunes: ADIPOKINES, PEROXISOME PROFILERATOR ACTIVATED RECEPTOR (PPAR) AGONISTS AND SEROTONIN. COMMON REGULATORS OF BONE AND FAT METABOLISM
377. Silje Engdal: HERBAL REMEDIES USED BY NORWEGIAN CANCER PATIENTS AND THEIR ROLE IN HERB-DRUG INTERACTIONS
378. Kristin Offerdal: IMPROVED ULTRASOUND IMAGING OF THE FETUS AND ITS CONSEQUENCES FOR SEVERE AND LESS SEVERE ANOMALIES
379. Øivind Rognmo: HIGH-INTENSITY AEROBIC EXERCISE AND CARDIOVASCULAR HEALTH
380. Jo-Åsmund Lund: RADIOTHERAPY IN ANAL CARCINOMA AND PROSTATE CANCER

2009

381. Tore Grüner Bjåstad: HIGH FRAME RATE ULTRASOUND IMAGING USING PARALLEL BEAMFORMING
382. Erik Søndenaa: INTELLECTUAL DISABILITIES IN THE CRIMINAL JUSTICE SYSTEM
383. Berit Rostad: SOCIAL INEQUALITIES IN WOMEN'S HEALTH, HUNT 1984-86 AND 1995-97, THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
384. Jonas Crosby: ULTRASOUND-BASED QUANTIFICATION OF MYOCARDIAL DEFORMATION AND ROTATION
385. Erling Tronvik: MIGRAINE, BLOOD PRESSURE AND THE RENIN-ANGIOTENSIN SYSTEM
386. Tom Christensen: BRINGING THE GP TO THE FOREFRONT OF EPR DEVELOPMENT
387. Håkon Bergseng: ASPECTS OF GROUP B STREPTOCOCCUS (GBS) DISEASE IN THE NEWBORN. EPIDEMIOLOGY, CHARACTERISATION OF INVASIVE STRAINS AND EVALUATION OF INTRAPARTUM SCREENING
388. Ronny Myhre: GENETIC STUDIES OF CANDIDATE TENE3S IN PARKINSON'S DISEASE
389. Torbjørn Moe Eggebø: ULTRASOUND AND LABOUR
390. Eivind Wang: TRAINING IS MEDICINE FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE
391. Thea Kristin Våtsveen: GENETIC ABERRATIONS IN MYELOMA CELLS
392. Thomas Jozefiak: QUALITY OF LIFE AND MENTAL HEALTH IN CHILDREN AND ADOLESCENTS: CHILD AND PARENT PERSPECTIVES
393. Jens Erik Slagsvold: N-3 POLYUNSATURATED FATTY ACIDS IN HEALTH AND DISEASE – CLINICAL AND MOLECULAR ASPECTS
394. Kristine Misund: A STUDY OF THE TRANSCRIPTIONAL REPRESSOR ICER. REGULATORY NETWORKS IN GASTRIN-INDUCED GENE EXPRESSION
395. Franco M. Impellizzeri: HIGH-INTENSITY TRAINING IN FOOTBALL PLAYERS. EFFECTS ON PHYSICAL AND TECHNICAL PERFORMANCE
396. Kari Hanne Gjeilo: HEALTH-RELATED QUALITY OF LIFE AND CHRONIC PAIN IN PATIENTS UNDERGOING CARDIAC SURGERY
397. Øyvind Hauso: NEUROENDOCRINE ASPECTS OF PHYSIOLOGY AND DISEASE
398. Ingvild Bjellmo Johnsen: INTRACELLULAR SIGNALING MECHANISMS IN THE INNATE IMMUNE RESPONSE TO VIRAL INFECTIONS

399. Linda Tømmerdal Roten: GENETIC PREDISPOSITION FOR DEVELOPMENT OF PREEMCLAMPSIA – CANDIDATE GENE STUDIES IN THE HUNT (NORD-TRØNDELAG HEALTH STUDY) POPULATION
400. Trude Teoline Nausthaug Rakvåg: PHARMACOGENETICS OF MORPHINE IN CANCER PAIN
401. Hanne Lehn: MEMORY FUNCTIONS OF THE HUMAN MEDIAL TEMPORAL LOBE STUDIED WITH fMRI
402. Randi Utne Holt: ADHESION AND MIGRATION OF MYELOMA CELLS – IN VITRO STUDIES –
403. Trygve Solstad: NEURAL REPRESENTATIONS OF EUCLIDEAN SPACE
404. Unn-Merete Fagerli: MULTIPLE MYELOMA CELLS AND CYTOKINES FROM THE BONE MARROW ENVIRONMENT; ASPECTS OF GROWTH REGULATION AND MIGRATION
405. Sigrid Bjørnelv: EATING– AND WEIGHT PROBLEMS IN ADOLESCENTS, THE YOUNG HUNT-STUDY
406. Mari Hoff: CORTICAL HAND BONE LOSS IN RHEUMATOID ARTHRITIS. EVALUATING DIGITAL X-RAY RADIOGRAMMETRY AS OUTCOME MEASURE OF DISEASE ACTIVITY, RESPONSE VARIABLE TO TREATMENT AND PREDICTOR OF BONE DAMAGE
407. Siri Bjørgen: AEROBIC HIGH INTENSITY INTERVAL TRAINING IS AN EFFECTIVE TREATMENT FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE
408. Susanne Lindqvist: VISION AND BRAIN IN ADOLESCENTS WITH LOW BIRTH WEIGHT
409. Torbjørn Hergum: 3D ULTRASOUND FOR QUANTITATIVE ECHOCARDIOGRAPHY
410. Jørgen Urnes: PATIENT EDUCATION IN GASTRO-OESOPHAGEAL REFLUX DISEASE. VALIDATION OF A DIGESTIVE SYMPTOMS AND IMPACT QUESTIONNAIRE AND A RANDOMISED CONTROLLED TRIAL OF PATIENT EDUCATION
411. Elvar Eyjolfsson: 13C NMRS OF ANIMAL MODELS OF SCHIZOPHRENIA
412. Marius Steiro Fimland: CHRONIC AND ACUTE NEURAL ADAPTATIONS TO STRENGTH TRAINING
413. Øyvind Støren: RUNNING AND CYCLING ECONOMY IN ATHLETES; DETERMINING FACTORS, TRAINING INTERVENTIONS AND TESTING
414. Håkon Hov: HEPATOCYTE GROWTH FACTOR AND ITS RECEPTOR C-MET. AUTOCRINE GROWTH AND SIGNALING IN MULTIPLE MYELOMA CELLS
415. Maria Radtke: ROLE OF AUTOIMMUNITY AND OVERSTIMULATION FOR BETA-CELL DEFICIENCY. EPIDEMIOLOGICAL AND THERAPEUTIC PERSPECTIVES
416. Liv Bente Romundstad: ASSISTED FERTILIZATION IN NORWAY: SAFETY OF THE REPRODUCTIVE TECHNOLOGY
417. Erik Magnus Berntsen: PREOPERATIV PLANNING AND FUNCTIONAL NEURONAVIGATION – WITH FUNCTIONAL MRI AND DIFFUSION TENSOR TRACTOGRAPHY IN PATIENTS WITH BRAIN LESIONS
418. Tonje Strømmen Steigedal: MOLECULAR MECHANISMS OF THE PROLIFERATIVE RESPONSE TO THE HORMONE GASTRIN
419. Vidar Rao: EXTRACORPOREAL PHOTOCHEMOTHERAPY IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA OR GRAFT-vs-HOST DISEASE
420. Torkild Visnes: DNA EXCISION REPAIR OF URACIL AND 5-FLUOROURACIL IN HUMAN CANCER CELL LINES

2010

421. John Munkhaugen: BLOOD PRESSURE, BODY WEIGHT, AND KIDNEY FUNCTION IN THE NEAR-NORMAL RANGE: NORMALITY, RISK FACTOR OR MORBIDITY ?
422. Ingrid Castberg: PHARMACOKINETICS, DRUG INTERACTIONS AND ADHERENCE TO TREATMENT WITH ANTIPSYCHOTICS: STUDIES IN A NATURALISTIC SETTING
423. Jian Xu: BLOOD-OXYGEN-LEVEL-DEPENDENT-FUNCTIONAL MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING IN TRAUMATIC BRAIN INJURY RESEARCH
424. Sigmund Simonsen: ACCEPTABLE RISK AND THE REQUIREMENT OF PROPORTIONALITY IN EUROPEAN BIOMEDICAL RESEARCH LAW. WHAT DOES THE REQUIREMENT THAT BIOMEDICAL RESEARCH SHALL NOT INVOLVE RISKS AND BURDENS DISPROPORTIONATE TO ITS POTENTIAL BENEFITS MEAN?

425. Astrid Woodhouse: MOTOR CONTROL IN WHIPLASH AND CHRONIC NON-TRAUMATIC NECK PAIN
426. Line Rørstad Jensen: EVALUATION OF TREATMENT EFFECTS IN CANCER BY MR IMAGING AND SPECTROSCOPY
427. Trine Moholdt: AEROBIC EXERCISE IN CORONARY HEART DISEASE
428. Øystein Olsen: ANALYSIS OF MANGANESE ENHANCED MRI OF THE NORMAL AND INJURED RAT CENTRAL NERVOUS SYSTEM
429. Bjørn H. Grønberg: PEMETREXED IN THE TREATMENT OF ADVANCED LUNG CANCER
430. Vigdis Schnell Husby: REHABILITATION OF PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY WITH FOCUS ON MUSCLE STRENGTH, WALKING AND AEROBIC ENDURANCE PERFORMANCE
431. Torbjørn Øien: CHALLENGES IN PRIMARY PREVENTION OF ALLERGY. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY.
432. Kari Anne Indredavik Evensen: BORN TOO SOON OR TOO SMALL: MOTOR PROBLEMS IN ADOLESCENCE
433. Lars Adde: PREDICTION OF CEREBRAL PALSY IN YOUNG INFANTS. COMPUTER BASED ASSESSMENT OF GENERAL MOVEMENTS
434. Magnus Fasting: PRE- AND POSTNATAL RISK FACTORS FOR CHILDHOOD ADIPOSITY
435. Vivi Talstad Monsen: MECHANISMS OF ALKYLATION DAMAGE REPAIR BY HUMAN AlkB HOMOLOGUES
436. Toril Skandsen: MODERATE AND SEVERE TRAUMATIC BRAIN INJURY. MAGNETIC RESONANCE IMAGING FINDINGS, COGNITION AND RISK FACTORS FOR DISABILITY
437. Ingeborg Smidesang: ALLERGY RELATED DISORDERS AMONG 2-YEAR OLDS AND ADOLESCENTS IN MID-NORWAY – PREVALENCE, SEVERITY AND IMPACT. THE PACT STUDY 2005, THE YOUNG HUNT STUDY 1995-97
438. Vidar Halsteinli: MEASURING EFFICIENCY IN MENTAL HEALTH SERVICE DELIVERY: A STUDY OF OUTPATIENT UNITS IN NORWAY
439. Karen Lehrmann Ægidius: THE PREVALENCE OF HEADACHE AND MIGRAINE IN RELATION TO SEX HORMONE STATUS IN WOMEN. THE HUNT 2 STUDY
440. Madelene Ericsson: EXERCISE TRAINING IN GENETIC MODELS OF HEART FAILURE
441. Marianne Klokk: THE ASSOCIATION BETWEEN SELF-REPORTED ECZEMA AND COMMON MENTAL DISORDERS IN THE GENERAL POPULATION. THE HORDALAND HEALTH STUDY (HUSK)
442. Tomas Ottemo Stølen: IMPAIRED CALCIUM HANDLING IN ANIMAL AND HUMAN CARDIOMYOCYTES REDUCE CONTRACTILITY AND INCREASE ARRHYTHMIA POTENTIAL – EFFECTS OF AEROBIC EXERCISE TRAINING
443. Bjarne Hansen: ENHANCING TREATMENT OUTCOME IN COGNITIVE BEHAVIOURAL THERAPY FOR OBSESSIVE COMPULSIVE DISORDER: THE IMPORTANCE OF COGNITIVE FACTORS
444. Mona Løvlien: WHEN EVERY MINUTE COUNTS. FROM SYMPTOMS TO ADMISSION FOR ACUTE MYOCARDIAL INFARCTION WITH SPECIAL EMPHASIS ON GENDER DIFFERECES
445. Karin Margaretha Gilljam: DNA REPAIR PROTEIN COMPLEXES, FUNCTIONALITY AND SIGNIFICANCE FOR REPAIR EFFICIENCY AND CELL SURVIVAL
446. Anne Byriel Walls: NEURONAL GLIAL INTERACTIONS IN CEREBRAL ENERGY – AND AMINO ACID HOMEOSTASIS – IMPLICATIONS OF GLUTAMATE AND GABA
447. Cathrine Fallang Knetter: MECHANISMS OF TOLL-LIKE RECEPTOR 9 ACTIVATION
448. Marit Følsvik Svindseth: A STUDY OF HUMILIATION, NARCISSISM AND TREATMENT OUTCOME IN PATIENTS ADMITTED TO PSYCHIATRIC EMERGENCY UNITS
449. Karin Elvenes Bakkelund: GASTRIC NEUROENDOCRINE CELLS – ROLE IN GASTRIC NEOPLASIA IN MAN AND RODENTS
450. Kirsten Brun Kjelstrup: DORSOVENTRAL DIFFERENCES IN THE SPATIAL REPRESENTATION AREAS OF THE RAT BRAIN
451. Roar Johansen: MR EVALUATION OF BREAST CANCER PATIENTS WITH POOR PROGNOSIS
452. Rigmor Myran: POST TRAUMATIC NECK PAIN. EPIDEMIOLOGICAL, NEURORADIOLOGICAL AND CLINICAL ASPECTS

453. Krisztina Kunszt Johansen: GENEALOGICAL, CLINICAL AND BIOCHEMICAL STUDIES IN *LRRK2* – ASSOCIATED PARKINSON'S DISEASE
454. Pål Gjerden: THE USE OF ANTICHOLINERGIC ANTIPARKINSON AGENTS IN NORWAY. EPIDEMIOLOGY, TOXICOLOGY AND CLINICAL IMPLICATIONS
455. Else Marie Huuse: ASSESSMENT OF TUMOR MICROENVIRONMENT AND TREATMENT EFFECTS IN HUMAN BREAST CANCER XENOGRAFTS USING MR IMAGING AND SPECTROSCOPY
456. Khalid S. Ibrahim: INTRAOPERATIVE ULTRASOUND ASSESSMENT IN CORONARY ARTERY BYPASS SURGERY – WITH SPECIAL REFERENCE TO CORONARY ANASTOMOSES AND THE ASCENDING AORTA
457. Bjørn Øglænd: ANTHROPOMETRY, BLOOD PRESSURE AND REPRODUCTIVE DEVELOPMENT IN ADOLESCENCE OF OFFSPRING OF MOTHERS WHO HAD PREECLAMPSIA IN PREGNANCY
458. John Olav Roaldset: RISK ASSESSMENT OF VIOLENT, SUICIDAL AND SELF-INJURIOUS BEHAVIOUR IN ACUTE PSYCHIATRY – A BIO-PSYCHO-SOCIAL APPROACH
459. Håvard Dalen: ECHOCARDIOGRAPHIC INDICES OF CARDIAC FUNCTION – NORMAL VALUES AND ASSOCIATIONS WITH CARDIAC RISK FACTORS IN A POPULATION FREE FROM CARDIOVASCULAR DISEASE, HYPERTENSION AND DIABETES: THE HUNT 3 STUDY
460. Beate André: CHANGE CAN BE CHALLENGING. INTRODUCTION TO CHANGES AND IMPLEMENTATION OF COMPUTERIZED TECHNOLOGY IN HEALTH CARE
461. Latha Nrugham: ASSOCIATES AND PREDICTORS OF ATTEMPTED SUICIDE AMONG DEPRESSED ADOLESCENTS – A 6-YEAR PROSPECTIVE STUDY
462. Håvard Bersås Nordgaard: TRANSIT-TIME FLOWMETRY AND WALL SHEAR STRESS ANALYSIS OF CORONARY ARTERY BYPASS GRAFTS – A CLINICAL AND EXPERIMENTAL STUDY

Cotutelle with University of Ghent: Abigail Emily Swillens: A MULTIPHYSICS MODEL FOR IMPROVING THE ULTRASONIC ASSESSMENT OF LARGE ARTERIES

2011

463. Marte Helene Bjørk: DO BRAIN RHYTHMS CHANGE BEFORE THE MIGRAINE ATTACK? A LONGITUDINAL CONTROLLED EEG STUDY
464. Carl-Jørgen Arum: A STUDY OF UROTHELIAL CARCINOMA: GENE EXPRESSION PROFILING, TUMORIGENESIS AND THERAPIES IN ORTHOTOPIC ANIMAL MODELS
465. Ingunn Harstad: TUBERCULOSIS INFECTION AND DISEASE AMONG ASYLUM SEEKERS IN NORWAY. SCREENING AND FOLLOW-UP IN PUBLIC HEALTH CARE
466. Leif Åge Strand: EPIDEMIOLOGICAL STUDIES AMONG ROYAL NORWEGIAN NAVY SERVICEMEN. COHORT ESTABLISHMENT, CANCER INCIDENCE AND CAUSE-SPECIFIC MORTALITY
467. Katrine Høyer Holgersen: SURVIVORS IN THEIR THIRD DECADE AFTER THE NORTH SEA OIL RIG DISASTER OF 1980. LONG-TERM PERSPECTIVES ON MENTAL HEALTH
468. Marianne Wallenius: PREGNANCY RELATED ASPECTS OF CHRONIC INFLAMMATORY ARTHRITIDES: DISEASE ONSET POSTPARTUM, PREGNANCY OUTCOMES AND FERTILITY. DATA FROM A NORWEGIAN PATIENT REGISTRY LINKED TO THE MEDICAL BIRTH REGISTRY OF NORWAY
469. Ole Vegard Solberg: 3D ULTRASOUND AND NAVIGATION – APPLICATIONS IN LAPAROSCOPIC SURGERY
470. Inga Ekeberg Schjerve: EXERCISE-INDUCED IMPROVEMENT OF MAXIMAL OXYGEN UPTAKE AND ENDOTHELIAL FUNCTION IN OBESE AND OVERWEIGHT INDIVIDUALS ARE DEPENDENT ON EXERCISE-INTENSITY
471. Eva Veslemøy Tyldum: CARDIOVASCULAR FUNCTION IN PREECLAMPSIA – WITH REFERENCE TO ENDOTHELIAL FUNCTION, LEFT VENTRICULAR FUNCTION AND PRE-PREGNANCY PHYSICAL ACTIVITY
472. Benjamin Garzón Jiménez de Cisneros: CLINICAL APPLICATIONS OF MULTIMODAL MAGNETIC RESONANCE IMAGING
473. Halvard Knut Nilsen: ASSESSING CODEINE TREATMENT TO PATIENTS WITH CHRONIC NON-MALIGNANT PAIN: NEUROPSYCHOLOGICAL FUNCTIONING, DRIVING ABILITY AND WEANING

474. Eiliv Brenner: GLUTAMATE RELATED METABOLISM IN ANIMAL MODELS OF SCHIZOPHRENIA
475. Egil Jonsbu: CHEST PAIN AND PALPITATIONS IN A CARDIAC SETTING; PSYCHOLOGICAL FACTORS, OUTCOME AND TREATMENT
476. Mona Høysæter Fenstad: GENETIC SUSCEPTIBILITY TO PREECLAMPSIA : STUDIES ON THE NORD-TRØNDELAG HEALTH STUDY (HUNT) COHORT, AN AUSTRALIAN/NEW ZEALAND FAMILY COHORT AND DECIDUA BASALIS TISSUE
477. Svein Erik Gaustad: CARDIOVASCULAR CHANGES IN DIVING: FROM HUMAN RESPONSE TO CELL FUNCTION
478. Karin Torvik: PAIN AND QUALITY OF LIFE IN PATIENTS LIVING IN NURSING HOMES
479. Arne Solberg: OUTCOME ASSESSMENTS IN NON-METASTATIC PROSTATE CANCER
480. Henrik Sahlin Pettersen: CYTOTOXICITY AND REPAIR OF URACIL AND 5-FLUOROURACIL IN DNA
481. Pui-Lam Wong: PHYSICAL AND PHYSIOLOGICAL CAPACITY OF SOCCER PLAYERS: EFFECTS OF STRENGTH AND CONDITIONING
482. Ole Solheim: ULTRASOUND GUIDED SURGERY IN PATIENTS WITH INTRACRANIAL TUMOURS
483. Sten Roar Snare: QUANTITATIVE CARDIAC ANALYSIS ALGORITHMS FOR POCKET-SIZED ULTRASOUND DEVICES
484. Marit Skyrud Bratlie: LARGE-SCALE ANALYSIS OF ORTHOLOGS AND PARALOGS IN VIRUSES AND PROKARYOTES
485. Anne Elisabeth F. Isern: BREAST RECONSTRUCTION AFTER MASTECTOMY – RISK OF RECURRENCE AFTER DELAYED LARGE FLAP RECONSTRUCTION – AESTHETIC OUTCOME, PATIENT SATISFACTION, QUALITY OF LIFE AND SURGICAL RESULTS; HISTOPATHOLOGICAL FINDINGS AND FOLLOW-UP AFTER PROPHYLACTIC MASTECTOMY IN HEREDITARY BREAST CANCER
486. Guro L. Andersen: CEREBRAL PALSY IN NORWAY – SUBTYPES, SEVERITY AND RISK FACTORS
487. Frode Kolstad: CERVICAL DISC DISEASE – BIOMECHANICAL ASPECTS
488. Bente Nordtug: CARING BURDEN OF COHABITANTS LIVING WITH PARTNERS SUFFERING FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE OR DEMENTIA
489. Mariann Gjervik Heldahl: EVALUATION OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER BASED ON MR METHODOLOGY
490. Lise Tevik Løvseth: THE SUBJECTIVE BURDEN OF CONFIDENTIALITY
491. Marie Hjelmseth Aune: INFLAMMATORY RESPONSES AGAINST GRAM NEGATIVE BACTERIA INDUCED BY TLR4 AND NLRP12
492. Tina Strømdal Wik: EXPERIMENTAL EVALUATION OF NEW CONCEPTS IN HIP ARTHROPLASTY
493. Solveig Sigurdardottir: CLINICAL ASPECTS OF CEREBRAL PALSY IN ICELAND. A POPULATION-BASED STUDY OF PRESCHOOL CHILDREN
494. Arne Reimers: CLINICAL PHARMACOKINETICS OF LAMOTRIGINE
495. Monica Wegling: KULTURMENNESKETS BYRDE OG SYKDOMMENS VELSIGNELSE. KAN MEDISINSK UTREDNING OG INTERVENSJON HA EN SELVSTENDIG FUNKSJON UAVHENGIG AV DET KURATIVE?
496. Silje Alvestad: ASTROCYTE-NEURON INTERACTIONS IN EXPERIMENTAL MESIAL TEMPORAL LOBE EPILEPSY – A STUDY OF UNDERLYING MECHANISMS AND POSSIBLE BIOMARKERS OF EPILEPTOGENESIS
497. Javaid Nauman: RESTING HEART RATE: A MATTER OF LIFE OR DEATH – PROSPECTIVE STUDIES OF RESTING HEART RATE AND CARDIOVASCULAR RISK (THE HUNT STUDY, NORWAY)
498. Thuy Nguyen: THE ROLE OF C-SRC TYROSINE KINASE IN ANTIVIRAL IMMUNE RESPONSES
499. Trine Naalsund Andreassen: PHARMACOKINETIC, PHARMACODYNAMIC AND PHARMACOGENETIC ASPECTS OF OXYCODONE TREATMENT IN CANCER PAIN
500. Eivor Alette Laugsand: SYMPTOMS IN PATIENTS RECEIVING OPIOIDS FOR CANCER PAIN – CLINICAL AND PHARMACOGENETIC ASPECTS

501. Dorthe Stensvold: PHYSICAL ACTIVITY, CARDIOVASCULAR HEALTH AND LONGEVITY IN PATIENTS WITH METABOLIC SYNDROME
502. Stian Thoresen Aspenes: PEAK OXYGEN UPTAKE AMONG HEALTHY ADULTS – CROSS-SECTIONAL DESCRIPTIONS AND PROSPECTIVE ANALYSES OF PEAK OXYGEN UPTAKE, PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK FACTORS IN HEALTHY ADULTS (20-90 YEARS)
503. Reidar Alexander Vigen: PATHOBIOLOGY OF GASTRIC CARCINOIDS AND ADENOCARCINOMAS IN RODENT MODELS AND PATIENTS. STUDIES OF GASTROCYSTOPLASTY, GENDER-RELATED FACTORS, AND AUTOPHAGY
504. Halvard Høilund-Kaupang: MODELS AND METHODS FOR INVESTIGATION OF REVERBERATIONS IN NONLINEAR ULTRASOUND IMAGING
505. Audhild Løhre: WELLBEING AMONG SCHOOL CHILDREN IN GRADES 1-10: PROMOTING AND ADVERSE FACTORS
506. Torgrim Tandstad: VOX POPULI. POPULATION-BASED OUTCOME STUDIES IN TESTICULAR CANCER
507. Anna Brenne Grønskag: THE EPIDEMIOLOGY OF HIP FRACTURES AMONG ELDERLY WOMEN IN NORD-TRØNDELAG. HUNT 1995-97, THE NORD-TRØNDELAG HEALTH STUDY
508. Kari Ravndal Risnes: BIRTH SIZE AND ADULT MORTALITY: A SYSTEMATIC REVIEW AND A LONG-TERM FOLLOW-UP OF NEARLY 40 000 INDIVIDUALS BORN AT ST. OLAV UNIVERSITY HOSPITAL IN TRONDHEIM 1920-1960
509. Hans Jakob Bøe: LONG-TERM POSTTRAUMATIC STRESS AFTER DISASTER – A CONTROLLED STUDY OF SURVIVORS' HEALTH 27 YEARS AFTER THE CAPSIZED NORTH SEA OIL RIG
510. Cathrin Barbara Canto, Cotutelle with University of Amsterdam: LAYER SPECIFIC INTEGRATIVE PROPERTIES OF ENTORHINAL PRINCIPAL NEURONS
511. Ioanna Sandvig: THE ROLE OF OLFACTORY ENSHEATHING CELLS, MRI, AND BIOMATERIALS IN TRANSPLANT-MEDIATED CNS REPAIR
512. Karin Fahl Wader: HEPATOCYTE GROWTH FACTOR, C-MET AND SYNDECAN-1 IN MULTIPLE MYELOMA
513. Gerd Tranø: FAMILIAL COLORECTAL CANCER
514. Bjarte Bergstrøm: INNATE ANTIVIRAL IMMUNITY – MECHANISMS OF THE RIG-I-MEDIATED RESPONSE
515. Marie Søfteland Sandvei: INCIDENCE, MORTALITY, AND RISK FACTORS FOR ANEURYSMAL SUBARACHNOID HEMORRHAGE. PROSPECTIVE ANALYZES OF THE HUNT AND TROMSØ STUDIES
516. Mary-Elizabeth Bradley Eilertsen: CHILDREN AND ADOLESCENTS SURVIVING CANCER: PSYCHOSOCIAL HEALTH, QUALITY OF LIFE AND SOCIAL SUPPORT
517. Takaya Saito: COMPUTATIONAL ANALYSIS OF REGULATORY MECHANISM AND INTERACTIONS OF MICRORNAS

Godkjent for disputas, publisert post mortem: Eivind Jullumstrø: COLORECTAL CANCER AT LEVANGER HOSPITAL 1980-2004

518. Christian Gutvik: A PHYSIOLOGICAL APPROACH TO A NEW DECOMPRESSION ALGORITHM USING NONLINEAR MODEL PREDICTIVE CONTROL
519. Ola Storrø: MODIFICATION OF ADJUVANT RISK FACTOR BEHAVIOURS FOR ALLERGIC DISEASE AND ASSOCIATION BETWEEN EARLY GUT MICROBIOTA AND ATOPIC SENSITIZATION AND ECZEMA. EARLY LIFE EVENTS DEFINING THE FUTURE HEALTH OF OUR CHILDREN
520. Guro Fanneløb Giskeødegård: IDENTIFICATION AND CHARACTERIZATION OF PROGNOSTIC FACTORS IN BREAST CANCER USING MR METABOLOMICS
521. Gro Christine Christensen Løhaugen: BORN PRETERM WITH VERY LOW BIRTH WEIGHT – NEVER ENDING COGNITIVE CONSEQUENCES?
522. Sigrid Nakrem: MEASURING QUALITY OF CARE IN NURSING HOMES – WHAT MATTERS?
523. Brita Pukstad: CHARACTERIZATION OF INNATE INFLAMMATORY RESPONSES IN ACUTE AND CHRONIC WOUNDS

2012

524. Hans H. Wasmuth: ILEAL POUCHES
525. Inger Økland: BIASES IN SECOND-TRIMESTER ULTRASOUND DATING RELATED TO PREDICTION MODELS AND FETAL MEASUREMENTS
526. Bjørn Mørkedal: BLOOD PRESSURE, OBESITY, SERUM IRON AND LIPIDS AS RISK FACTORS OF ISCHAEMIC HEART DISEASE
527. Siver Andreas Moestue: MOLECULAR AND FUNCTIONAL CHARACTERIZATION OF BREAST CANCER THROUGH A COMBINATION OF MR IMAGING, TRANSCRIPTOMICS AND METABOLOMICS
528. Guro Aune: CLINICAL, PATHOLOGICAL, AND MOLECULAR CLASSIFICATION OF OVARIAN CARCINOMA
529. Ingrid Alsos Lian: MECHANISMS INVOLVED IN THE PATHOGENESIS OF PRE-ECLAMPSIA AND FETAL GROWTH RESTRICTION. TRANSCRIPTIONAL ANALYSES OF PLACENTAL AND DECIDUAL TISSUE
530. Karin Solvang-Garten: X-RAY REPAIR CROSS-COMPLEMENTING PROTEIN 1 – THE ROLE AS A SCAFFOLD PROTEIN IN BASE EXCISION REPAIR AND SINGLE STRAND BREAK REPAIR
531. Toril Holien: BONE MORPHOGENETIC PROTEINS AND MYC IN MULTIPLE MYELOMA
532. Rooyen Mavenyengwa: *STREPTOCOCCUS AGALACTIAE* IN PREGNANT WOMEN IN ZIMBABWE: EPIDEMIOLOGY AND SEROTYPE MARKER CHARACTERISTICS
533. Tormod Rimehaug: EMOTIONAL DISTRESS AND PARENTING AMONG COMMUNITY AND CLINIC PARENTS
534. Maria Dung Cao: MR METABOLIC CHARACTERIZATION OF LOCALLY ADVANCED BREAST CANCER – TREATMENT EFFECTS AND PROGNOSIS
535. Mirta Mittelstedt Leal de Sousa: PROTEOMICS ANALYSIS OF PROTEINS INVOLVED IN DNA BASE REPAIR AND CANCER THERAPY
536. Halfdan Petursson: THE VALIDITY AND RELEVANCE OF INTERNATIONAL CARDIOVASCULAR DISEASE PREVENTION GUIDELINES FOR GENERAL PRACTICE
537. Marit By Rise: LIFTING THE VEIL FROM USER PARTICIPATION IN CLINICAL WORK – WHAT IS IT AND DOES IT WORK?
538. Lene Thoresen: NUTRITION CARE IN CANCER PATIENTS. NUTRITION ASSESSMENT: DIAGNOSTIC CRITERIA AND THE ASSOCIATION TO SURVIVAL AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ADVANCED COLORECTAL CARCINOMA
539. Berit Doseth: PROCESSING OF GENOMIC URACIL IN MAN AND MOUSE
540. Gro Falkenér Bertheussen: PHYSICAL ACTIVITY AND HEALTH IN A GENERAL POPULATION AND IN CANCER SURVIVORS – METHODOLOGICAL, OBSERVATIONAL AND CLINICAL ASPECTS
541. Anne Kari Knudsen: CANCER PAIN CLASSIFICATION
542. Sjur Urdson Gjerald: A FAST ULTRASOUND SIMULATOR
543. Harald Edvard Mølmen Hansen: CARDIOVASCULAR EFFECTS OF HIGH INTENSITY AEROBIC INTERVAL TRAINING IN HYPERTENSITIVE PATIENTS, HEALTHY AGED AND YOUNG PERSONS
544. Sasha Gulati: SURGICAL RESECTION OF HIGH-GRADE GLIOMAS
545. John Chr. Fløvig: FREQUENCY AND EFFECT OF SUBSTANCES AND PSYCHOACTIVE MEDICATIONS THE WEEK BEFORE ADMISSION TO AN ACUTE PSYCHIATRIC DEPARTMENT
546. Kristin Moksnes Husby: OPTIMIZING OPIOID TREATMENT FOR CANCER PAIN – CLINICAL AND PHARMACOLOGICAL ASPECTS
547. Audun Hanssen-Bauer: X-RAY REPAIR CROSS-COMPLEMENTING PROTEIN 1 ASSOCIATED MULTIPROTEIN COMPLEXES IN BASE EXCISION REPAIR
548. Marit Saunes: ECZEMA IN CHILDREN AND ADOLESCENTS – EPIDEMIOLOGY, COURSE AND IMPACT. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY, YOUNG-HUNT 1995-97
549. Guri Kaurstad: CARDIOMYOCYTE FUNCTION AND CALCIUM HANDLING IN ANIMAL MODELS OF INBORN AND ACQUIRED MAXIMAL OXYGEN UPTAKE

550. Kristian Svendsen: METHODOLOGICAL CHALLENGES IN PHARMACOEPIDEMIOLOGICAL STUDIES OF OPIOID CONSUMPTION
551. Signe Nilssen Stafne: EXERCISE DURING PREGNANCY
552. Marius Widerøe: MAGNETIC RESONANCE IMAGING OF HYPOXIC-ISCHEMIC BRAIN INJURY DEVELOPMENT IN THE NEWBORN RAT – MANGANESE AND DIFFUSION CONTRASTS
553. Andreas Radtke: MOLECULAR METHODS FOR TYPING *STREPTOCOCCUS AGALACTIAE* WITH SPECIAL EMPHASIS ON THE DEVELOPMENT AND VALIDATION OF A MULTI-LOCUS VARIABLE NUMBER OF TANDEM REPEATS ASSAY (MLVA)
554. Thor Wilhelm Bjelland: PHARMACOLOGICAL ASPECTS OF THERAPEUTIC HYPOTHERMIA
555. Caroline Hild Hakvåg Pettersen: THE EFFECT OF OMEGA-3 POLYUNSATURATED FATTY ACIDS ON HUMAN CANCER CELLS – MOLECULAR MECHANISMS INVOLVED
556. Inga Thorsen Vengen: INFLAMMATION AND ATHEROSCLEROSIS – RISK ASSOCIATIONS IN THE HUNT SURVEYS
557. Elisabeth Balstad Magnussen: PREECLAMPSIA, PRETERM BIRTH AND MATERNAL CARDIOVASCULAR RISK FACTORS
558. Monica Unsgaard-Tøndel: MOTOR CONTROL EXERCISES FOR PATIENTS WITH LOW BACK PAIN
559. Lars Erik Sande Laugsand: INSOMNIA AND RISK FOR CARDIOVASCULAR DISEASE
560. Kjersti Grønning: PATIENT EDUCATION AND CHRONIC INFLAMMATORY POLYARTHRITIS – COPING AND EFFECT
561. Hanne Gro Wenzel: PRE AND POST-INJURY HEALTH IN PERSONS WITH WHIPLASH: THE HUNT STUDY. EXPLORATION OF THE FUNCTIONAL SOMATIC MODEL FOR CHRONIC WHIPLASH
562. Øystein Grimstad: TOLL-LIKE RECEPTOR-MEDIATED INFLAMMATORY RESPONSES IN KERATINOCYTES
563. Håkon Olav Leira: DEVELOPMENT OF AN IMAGE GUIDANCE RESEARCH SYSTEM FOR BRONCHOSCOPY
564. Michael A. Lang: DIVING IN EXTREME ENVIRONMENTS: THE SCIENTIFIC DIVING EXPERIENCE
565. Helena Bertilsson: PROSTATE CANCER-TRANSLATIONAL RESEARCH. OPTIMIZING TISSUE SAMPLING SUITABLE FOR HISTOPATHOLOGIC, TRANSCRIPTOMIC AND METABOLIC PROFILING
566. Kirsten M. Selnæs: MR IMAGING AND SPECTROSCOPY IN PROSTATE AND COLON CANCER DIAGNOSTICS
567. Gunvor Steine Fosnes: CONSTIPATION AND DIARRHOEA. EFFECTIVENESS AND ADVERSE EFFECTS OF DRUGS
568. Areej Elkamil: SPASTIC CEREBRAL PALSY: RISK FACTORS, BOTULINUM TOXIN USE AND PREVENTION OF HIP DISLOCATION
569. Ruth Derdikman Eiron: SYMPTOMS OF ANXIETY AND DEPRESSION AND PSYCHOSOCIAL FUNCTION IN MALES AND FEMALES FROM ADOLESCENCE TO ADULTHOOD: LONGITUDINAL FINDINGS FROM THE NORD-TRØNDELAG HEALTH STUDY
570. Constantin Sergiu Jianu: PROTON PUMP INHIBITORS AND GASTRIC NEOPLASIA IN MAN
571. Øystein Finset Sørdal: THE ROLE OF GASTRIN AND THE ECL CELL IN GASTRIC CARCINOGENESIS
572. Lisbeth Østgaard Rygg: GROUP EDUCATION FOR PATIENTS WITH TYPE 2 DIABETES – NEEDS, EXPERIENCES AND EFFECTS
573. Viola Lobert: IDENTIFICATION OF NOVEL REGULATORS OF EPITHELIAL POLARITY AND CELL MIGRATION
574. Maria Tunset Grinde: CHARACTERIZATION OF BREAST CANCER USING MR METABOLOMICS AND GENE EXPRESSION ANALYSIS
575. Grete Kjelvik: HUMAN ODOR IDENTIFICATION STUDIES IN HEALTHY INDIVIDUALS, MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE
576. Tor Eivind Bernstein: RECTAL CANCER SURGERY. PROGNOSTIC FACTORS RELATED TO TREATMENT

577. Kari Sand: INFORMED CONSENT DOCUMENTS FOR CANCER RESEARCH: TEXTUAL AND CONTEXTUAL FACTORS OF RELEVANCE FOR UNDERSTANDING
578. Laurent Francois Thomas: EFFECTS OF SINGLE-NUCLEOTIDE POLYMORPHISMS ON microRNA-BASED GENE REGULATION AND THEIR ASSOCIATION WITH DISEASE
579. Øystein Sandanger: THE INNATE IMMUNE SYSTEM: A PARADOXICAL MEDIATOR OF HOST DEFENSE, TISSUE REPAIR AND COLLATERAL DAMAGE
580. Line Knutsen Lund: MENTAL HEALTH IN LOW BIRTH WEIGHT INDIVIDUALS APPROACHING ADULTHOOD
581. Nils Kristian Skjærvold: AUTOMATED BLOOD GLUCOSE CONTROL – DEVELOPMENT AND TESTING OF AN ARTIFICIAL ENDOCRINE PANCREAS USING AV NOVEL INTRAVASCULAR GLUCOSE MONITOR AND A NEW APPROACH TO INSULIN PHARMACOLOGY
582. Håvard Kallestad: SLEEP DISTURBANCE: CLINICAL SIGNIFICANCE IN MENTAL HEALTH CARE AND COGNITIVE FACTORS
583. Anders Wallenius: URACIL-DNA GLYCOSYLASE, ACTIVATION-INDUCED DEAMINASE AND REGULATION OF ADAPTIVE IMMUNE RESPONSES
584. Gry Børmark Hoftun: CHRONIC NON-SPECIFIC PAIN IN ADOLESCENCE PREVALENCE, DISABILITY, AND ASSOCIATED FACTORS – YOUNG-HUNT AND HUNT 3, 2006-2008
585. Elisabeth Hansen: THE SIGNIFICANCE OF RESISTANCE TRAINING AND PSYCHOBIOLOGY IN PRIMARY PREVENTION OF TYPE 2 DIABETES AMONG PEOPLE WITH IMPAIRED GLUCOSE TOLERANCE
586. Ragnhild Omli: URINARY INCONTINENCE AND URINARY TRACT INFECTIONS IN THE ELDERLY: RISK FACTORS AND CONSEQUENCES
587. Christina Sæten Fjeldbo: GASTRIN-MEDIATED REGULATION OF GENE EXPRESSION; A SYSTEMS BIOLOGY APPROACH
588. Yunita Widyastuti: RISK FACTORS FOR COMMON COMPLICATIONS FOLLOWING ADULT HEART SURGERY
589. Anders Thorstensen: 2D AND 3D ECHOCARDIOGRAPHY DURING INOTROPIC ALTERATIONS AND AFTER RECENT MYOCARDIAL INFARCTION
590. Torstein Schrøder-Aasen: EFFECTS OF PURPLE CONEFLOWER (ECHINACEA PURPUREA) ON CYP3A4 METABOLISM AND P-GLYCOPROTEIN MEDIATED TRANSPORT *IN VITRO*