CHALLENGES IN DRUG DISCOVERY FROM MEDICINAL PLANTS

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The history of the use of medicinal plants

- Plants have been used as medicines for thousands of years.
- These medicines initially took the form of crude drugs such as tinctures, teas, poultices, powders, and other herbal formulations.
- The specific plants to be used and the methods of application for particular ailments were passed down through oral history.
- Eventually information regarding medicinal plants was recorded in herbals.
- In more recent history, the use of plants as medicines has involved the isolation of active compounds, beginning with the isolation of morphine from opium in the early 19th century.
- Drug discovery from medicinal plants led to the isolation of early drugs such as cocaine, codeine, digitoxin, and quinine, in addition to morphine, of which some are still in use.
- Isolation and characterization of pharmacologically active compounds from medicinal plants continue today. More recently, drug discovery techniques have been applied to the standardization of herbal medicines, to elucidate analytical marker compounds. The following provides a brief presentation of the importance of medicinal plants in drug discovery including noteworthy compounds isolated from this source, our research involving drug discovery using medicinal plants, and finally current challenges in regard to medicinal plant drug discovery.

Current research in drug discovery

- Current research in drug discovery from medicinal plants involves a multipurpose approach combining botanical, phytochemical, biological, and molecular techniques.
- Medicinal plant drug discovery continues to provide new and important leads against various pharmacological targets including cancer, HIV/AIDS, Alzheimer's, malaria, and pain.
- Our group has also isolated several compounds, mainly from edible plant species or plants used as dietary supplements and participated in the creation of a new generation of dosage forms .
- Although drug discovery from medicinal plants continues to provide an important source of new drug leads, numerous challenges are encountered including the procurement of plant materials, the selection and implementation of appropriate high-throughput screening bioassays, and the scale-up of active compounds

Introduction

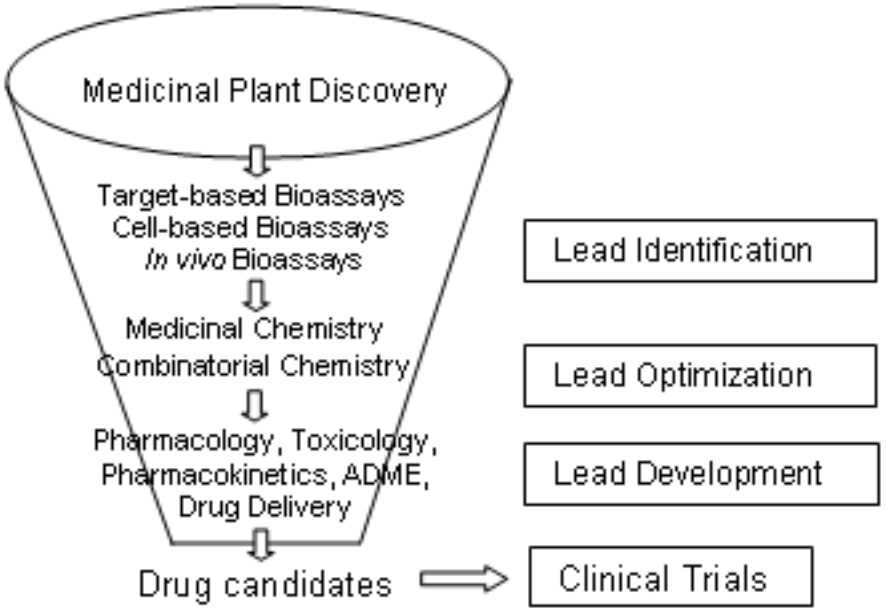
- There are many reasons that drugs fail to reach the market, including toxicity, lack of efficacy and marketing.
- It is also striking that about 40% of development compounds fail to reach the market due to poor pharmaceutical properties as a result of poor solubility, permeability and metabolic stability

Schematic of typical medicinal plant drug discovery and development

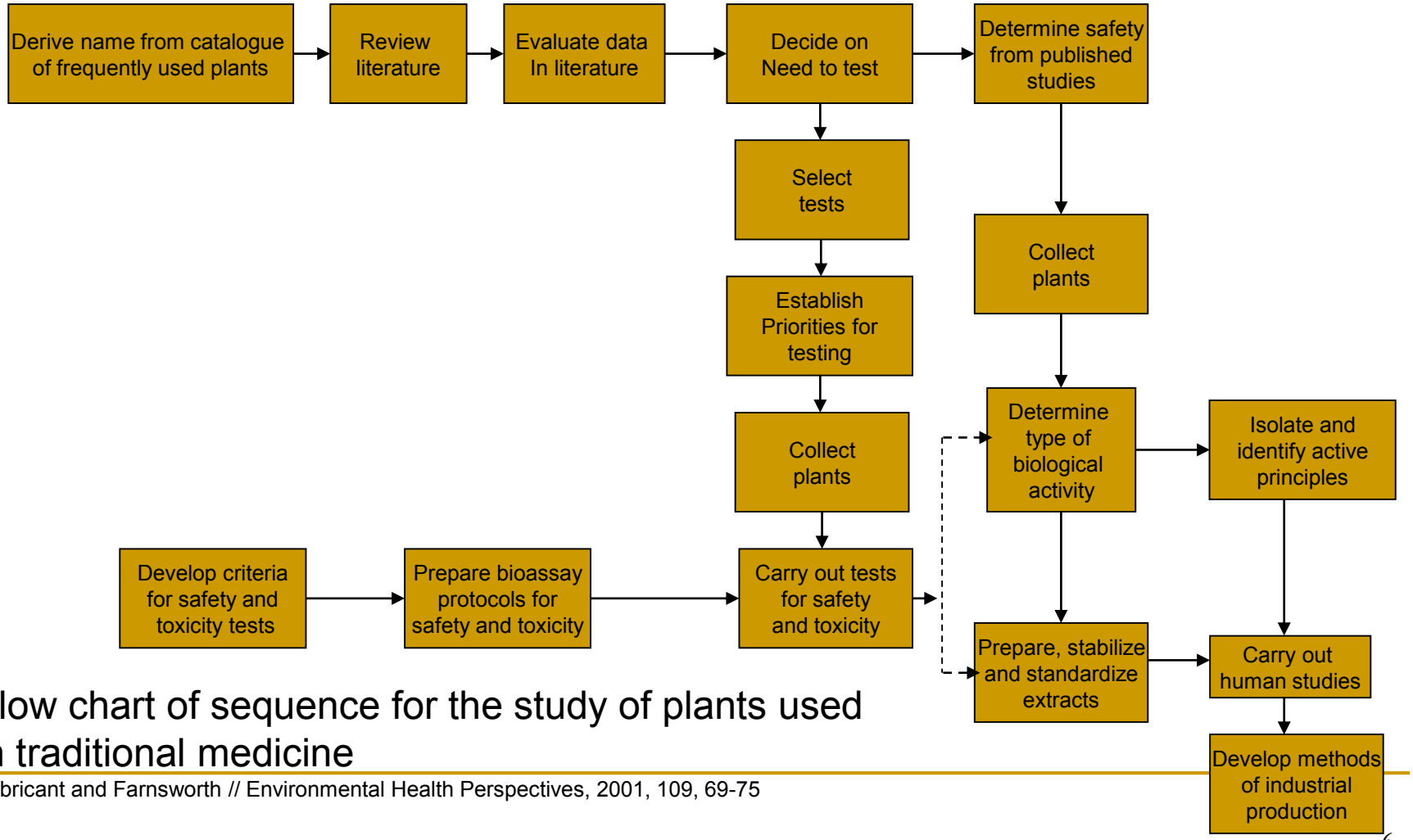
This drives pharmaceutical companies to profile drug-like properties as early as possible and increase the success rate of compounds to the market. Despite the evident successes of drug discovery from medicinal plants, future endeavors face many challenges. Pharmacognosists, phytochemists, and other natural product scientists will need to continuously improve the quality and quantity of compounds that enter the drug development phase to keep pace with other drug discovery efforts.

Lead identification is the first step in a lengthy drug development process.

Lead optimization (involving medicinal and combinatorial chemistry), lead development (including pharmacology, toxicology, pharmacokinetics, ADME [absorption, distribution, metabolism, and excretion], and drug delivery), and clinical trials all take a considerable length of time.



In 1985 it was proposed an approach, based on ethnomedical information, to experimentally pursue plants as a source of drugs. The possibility of drug development in the form of stable, standardized crude extracts and eventual development of the active principles from these plants was envisioned.

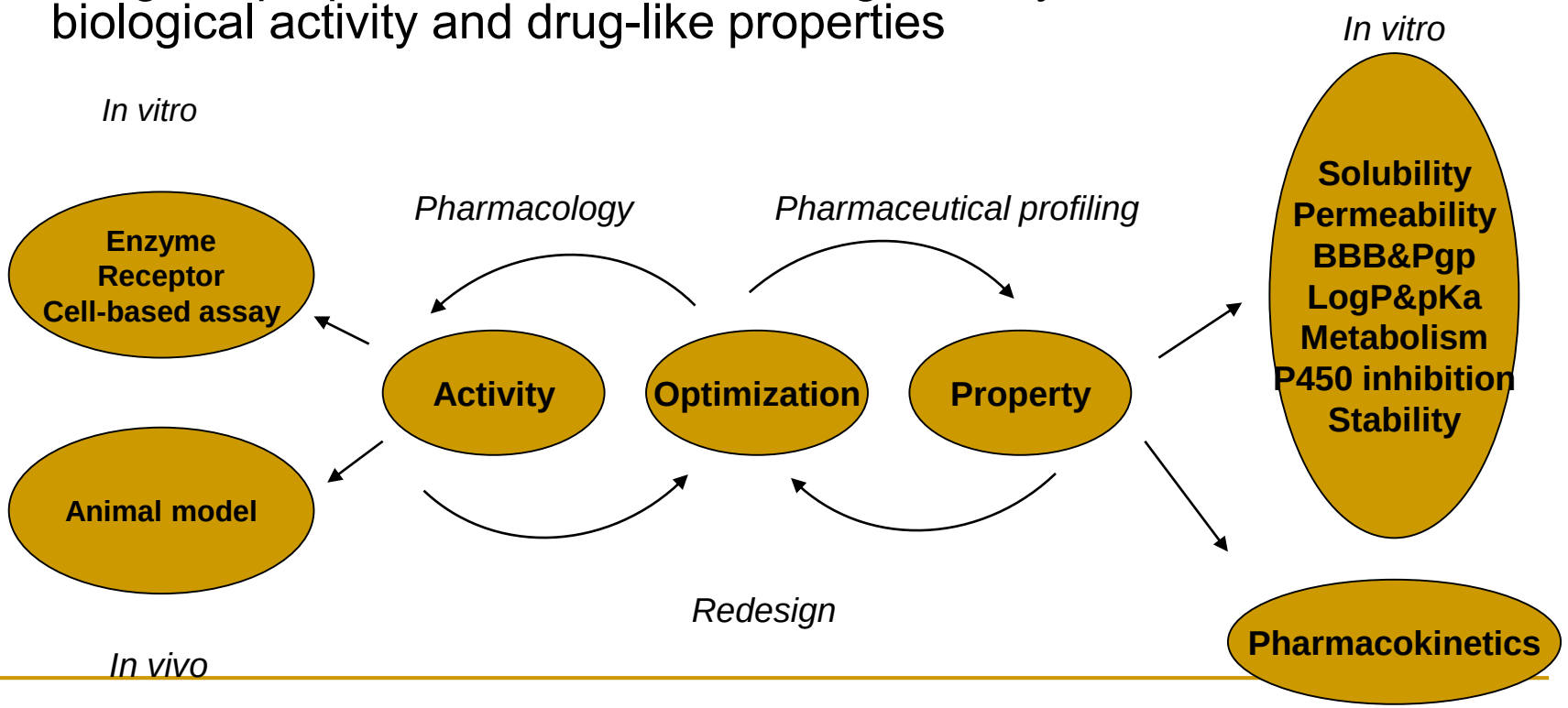


Flow chart of sequence for the study of plants used in traditional medicine

Fabricant and Farnsworth // Environmental Health Perspectives, 2001, 109, 69-75

Parallel optimization of activity and drug-like properties

- With the advance of drug discovery technologies, many new tools became available to help discovery scientists find better drugs faster. In the 1990s, new approaches were introduced for molecular biology, genomics, proteomics, combinatorial chemistry, high-throughput screening (HTS) and molecular modeling. 'Property-based design' is another new approach in discovery that deals with 'druglike' properties. A successful drug is really a combination of biological activity and drug-like properties



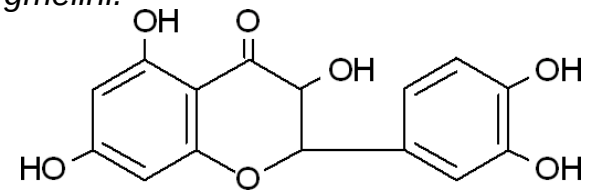
Impact of pharmaceutical profiling assays in drug discovery

Assays	Methods	Impact in drug discovery
Integrity	LC-MS	Start SAR with known purity and correct structure
Aggregation	DLS, EM	Avoid following the non-specific hits
Solubility	Direct UV Turbiditimetry	Interpret in vitro/in vivo assay results Enhance oral bioavailability Develop formulation strategy and potential salt forms
Permeability	Caco-2 PAMPA	Enhance oral absorption Interpret cell-based assay results
Lipophilicity	HPLC	Predict ADME/TOX properties
pKa	SGA	Predict effect of pH on solubility and permeability
CYP450 inhibition	Fluorescence, LC-MS-MS, Radiometric	Minimize toxicity due to drug–drug interactions

Property screening in parallel with activity screening allows medicinal chemists to optimize biological activities as well as drug-like properties. This approach has been widely accepted and implemented in pharmaceutical companies. This presentation discusses pharmaceutical profiling assays and their applications in drug discovery research.

Some examples of drugs from plants that served as models for the next generation of drugs are exemplified as follows:

Taxifolin (2β(R), 3α(S)-3',4',5,7-tetrahydroxyflavanonol, syn. **Dihydroquercetin**) for the first time was isolated from the rind of *Larix sibirica* and Larix *gmelini.*



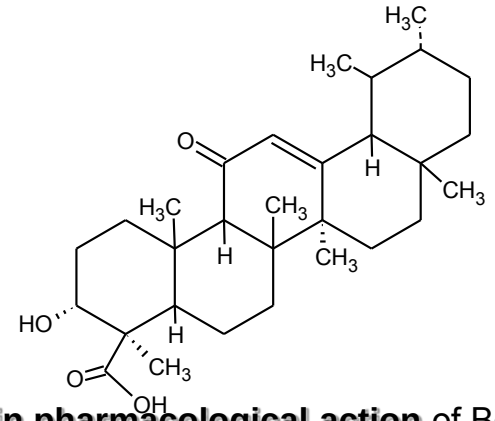
- significantly dilates blood vessel,
- improves microcirculation,
- increases cerebral blood flow,
- inhibits platelet aggregation activity

Biological activity of Taxifolin:

- Antithrombotic effect
- Anti-inflammatory effect
- Capillaroprotective effect
- Hepatoprotective effect
- Antioxidative effect

Dry extract of *Boswellia serrata*

Pharmacological effects are mainly attributed to the presence of the pentacyclic triterpenoids known as boswellic acids: β-boswellic, acetyl-β-boswellic, 11-keto-β-boswellic and acetyl-11-keto-β-boswellic.



The main pharmacological action of Boswellia extract is anti-inflammatory activity and anti-arthritis action. It has sedative, antibacterial, analgesic, antiseptic actions.

Formulation of poorly water-soluble drugs for oral administration

Lipid formulations

- Simple solutions
- self-emulsifying drug delivery systems (SEDDS)
- self-microemulsifying drug delivery systems (SMEDDS)
- systems with very little oil and disperse to form micellar solutions

Amorphous formulations

- Solid dispersions (with water-soluble polymers, e.g., polyethylene glycol, polyvinylpyrrolidone)
- Inclusion complexes (with e.g. ß-cyclodextrin)

Fundamental factors affecting oral drug absorption

- Physiological factors

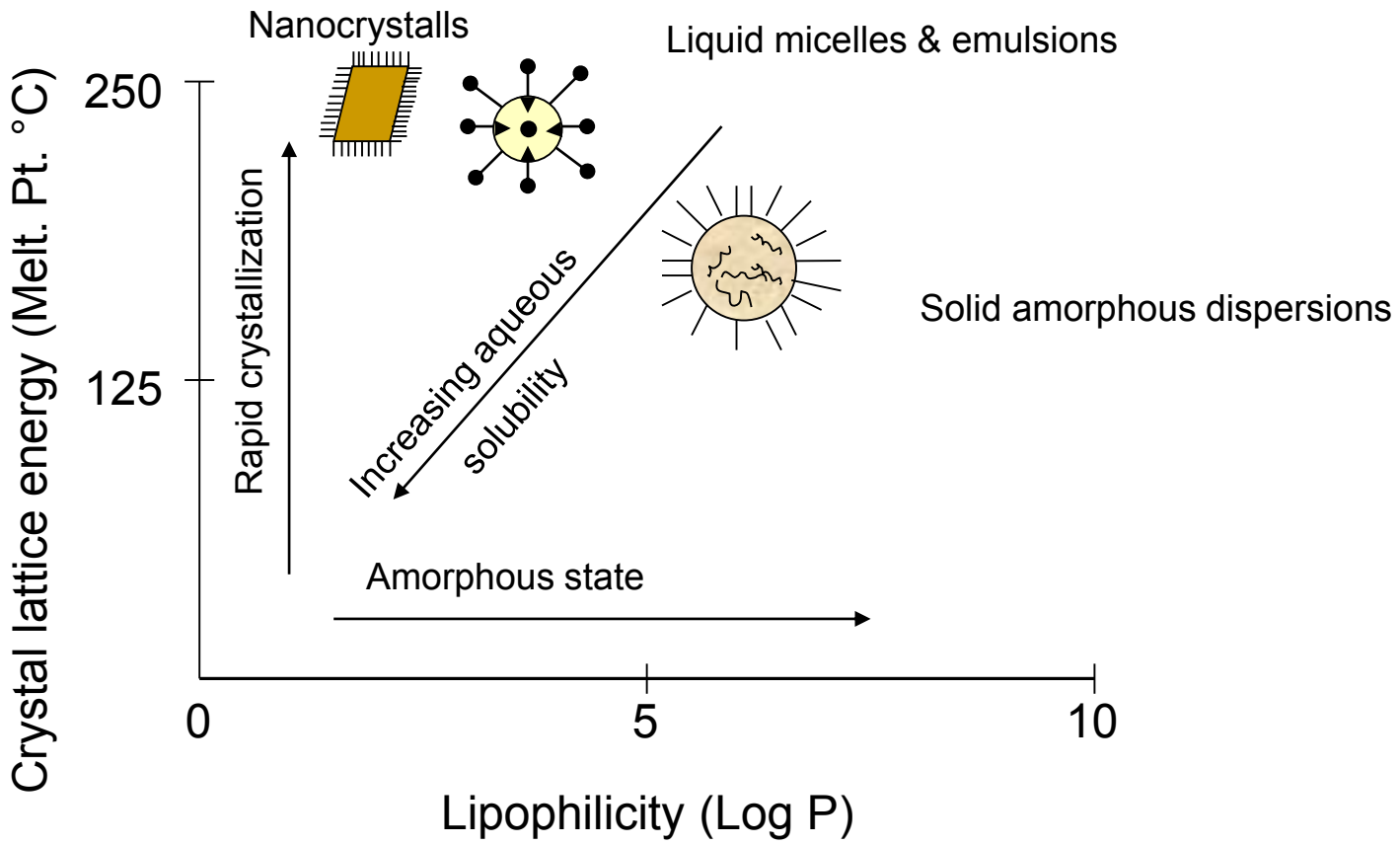
  The absorption of drug substances, delivered orally, will be highly dependant upon a wide range of physiological factors associated with the absorptive site(s) in the gastrointestinal (GI) tract (e.g, GI pH, gastric emptying rate, intestinal motility, blood flow, GI mucin and bile, and co-ingested food).
- Physicochemical factors
- Dosage form

A large amount of attention is rightly given to drug solubility but there are a number of other physicochemical factors that can radically effect absorption. These include lipophilicity, ionization and chemical stability in the GI tract.

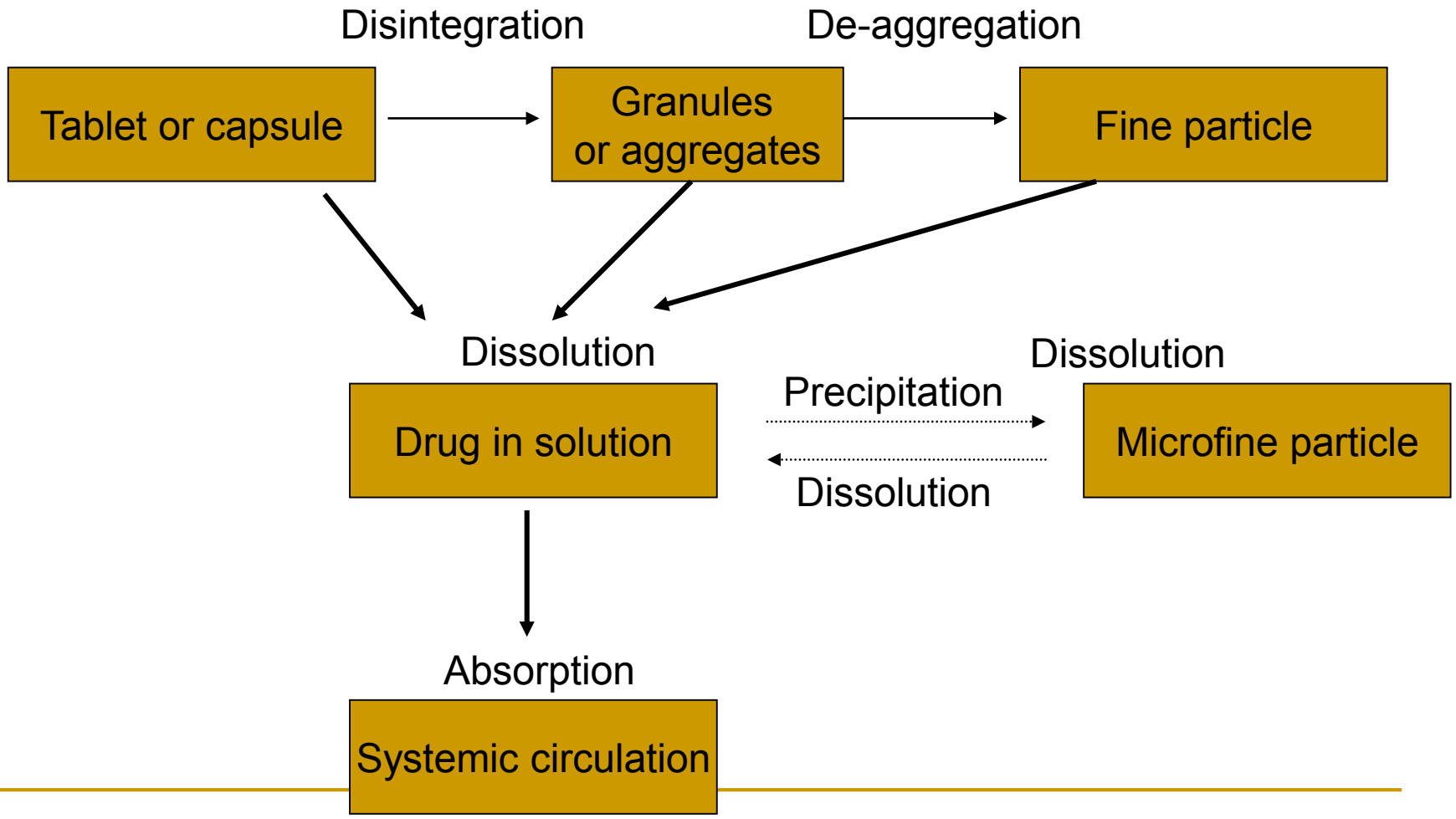
Factors influencing solubility include:

- the physical form of the drug substance (e.g., intrinsic polymorphism, crystallinity)
- salt formation (and the form of the salt)
- concentration of native surface active agents (such as bile salts)
- influence of co-ingested foods, particularly fatty foods (these in turn can affect the GI pH and assist dissolution through solubilisation / complexation)
- potential of the drug to ionize (pKa)

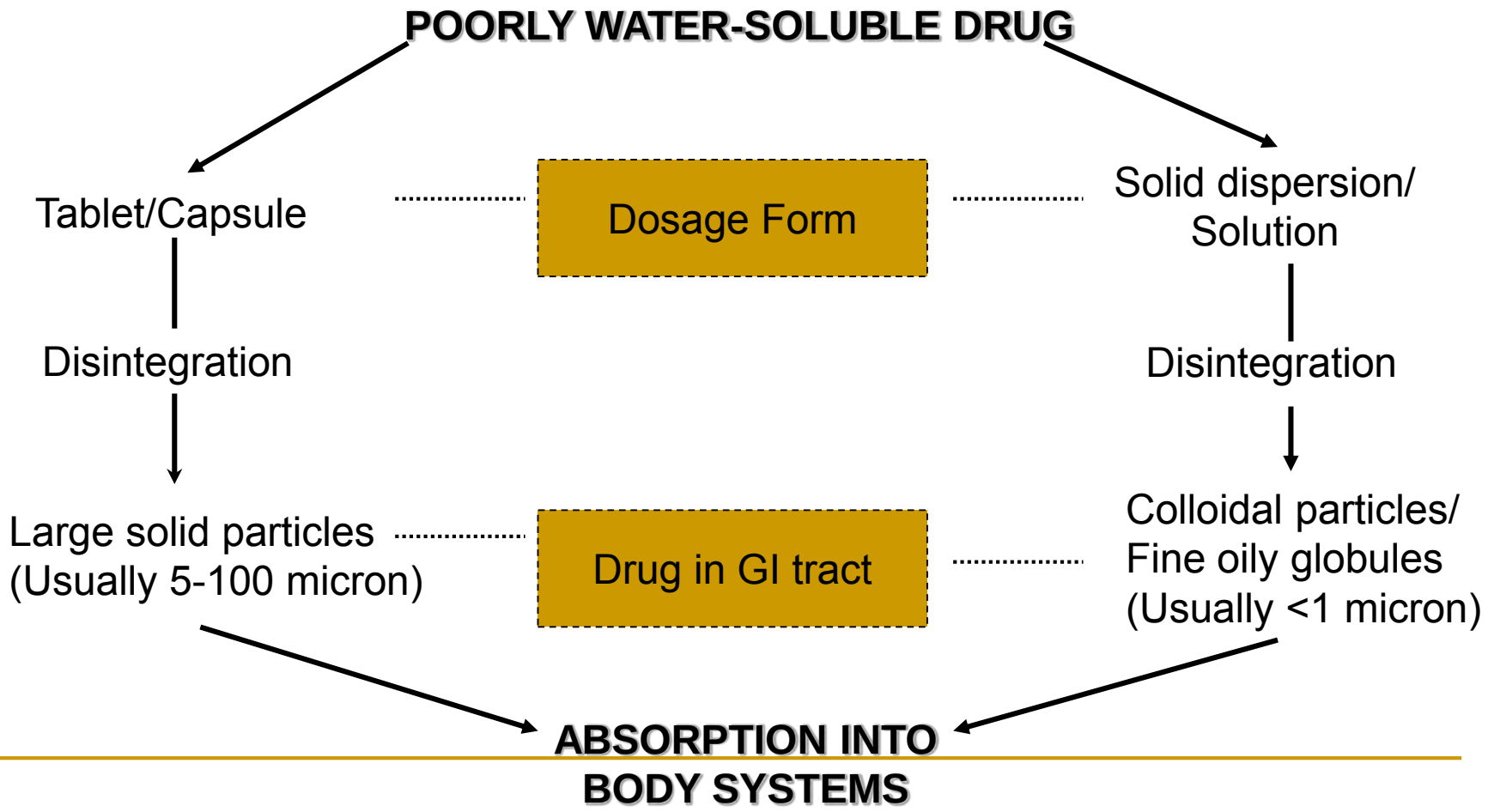
Physical properties of drugs with low solubility and relationship to some enabling technologies



The drug absorption process (schematic)



Schematic representation of the advantage of a solid dispersion formulation over the conventional tablet or capsule formulation



Biological activity of Taxifolin

- Antioxidative effect
- Antithrombotic effect
- Hepatoprotective effect
- Anti-inflammatory effect
- Capillaroprotective effect

Taxifolin is a component of medicines and some food supplements

Disadvantages of Taxifolin

- slightly soluble in water
- slow dissolution rate from solid oral forms
- effectiveness of taxifolin was discounted by its poor water solubility and low bioavailability after oral administration

Taxifolin Drug Discovery

Amorphous formulations

- Solid dispersions by melting method with PEG
- Solid dispersions by solvent method with PVP

The differential scanning calorimetry and microscopy data were applied to estimate the physical state and interactions of taxifolin with polymers.

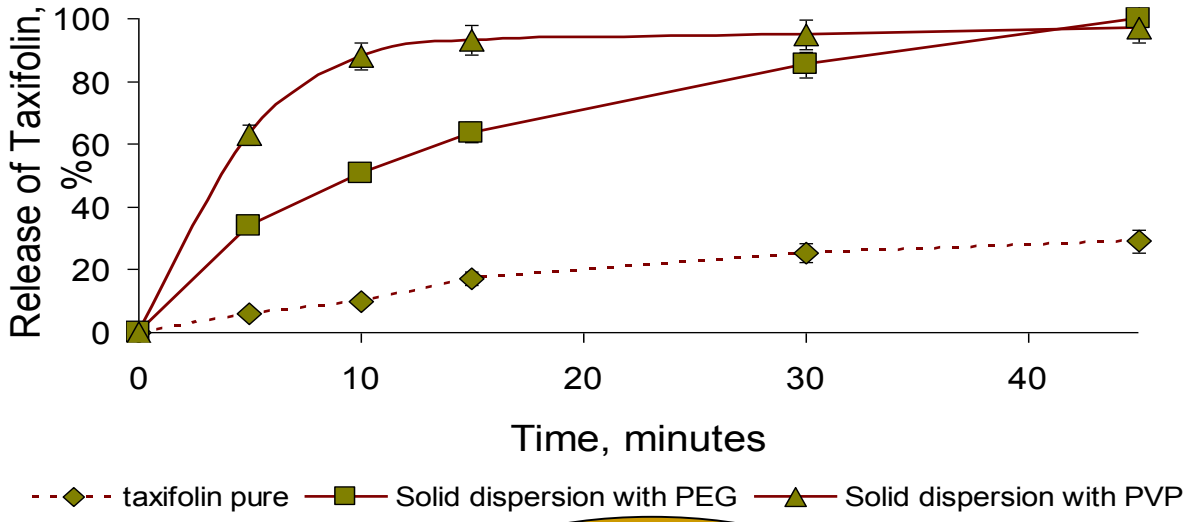
Lipid formulations

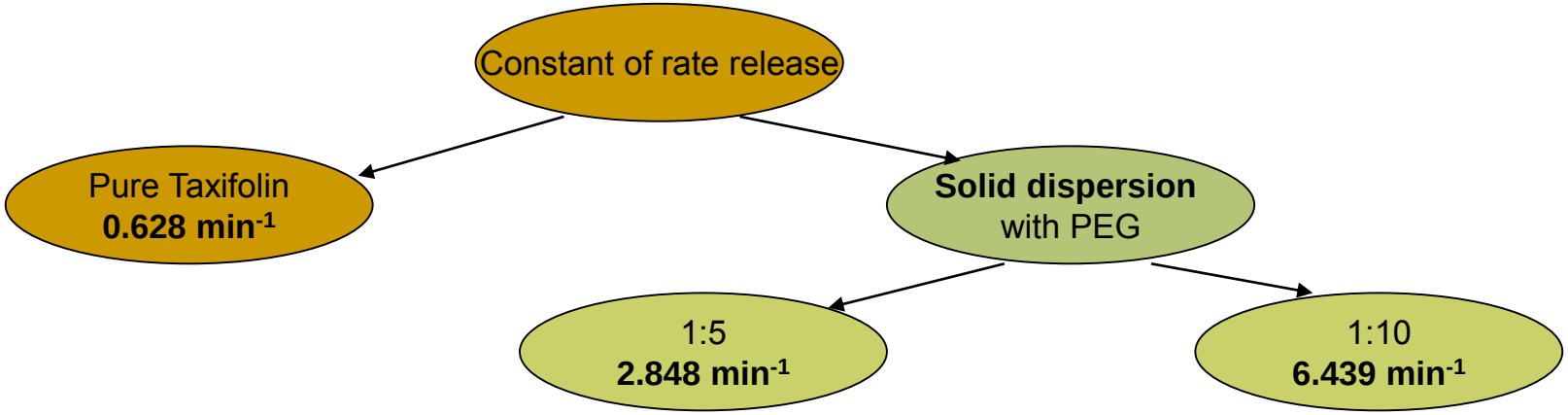
- self-microemulsifying drug delivery systems (SMEDDS)
- systems with very little oil and disperse to form micellar solutions

Study of rheology behavior of SMEDDS of Taxifolin was shown, that our microemulsion is Newtonian liquid as its viscosity does not depend on a gradient of rate. Thus the developed system of drug delivery has "ideal" character of current.

In vitro testing:

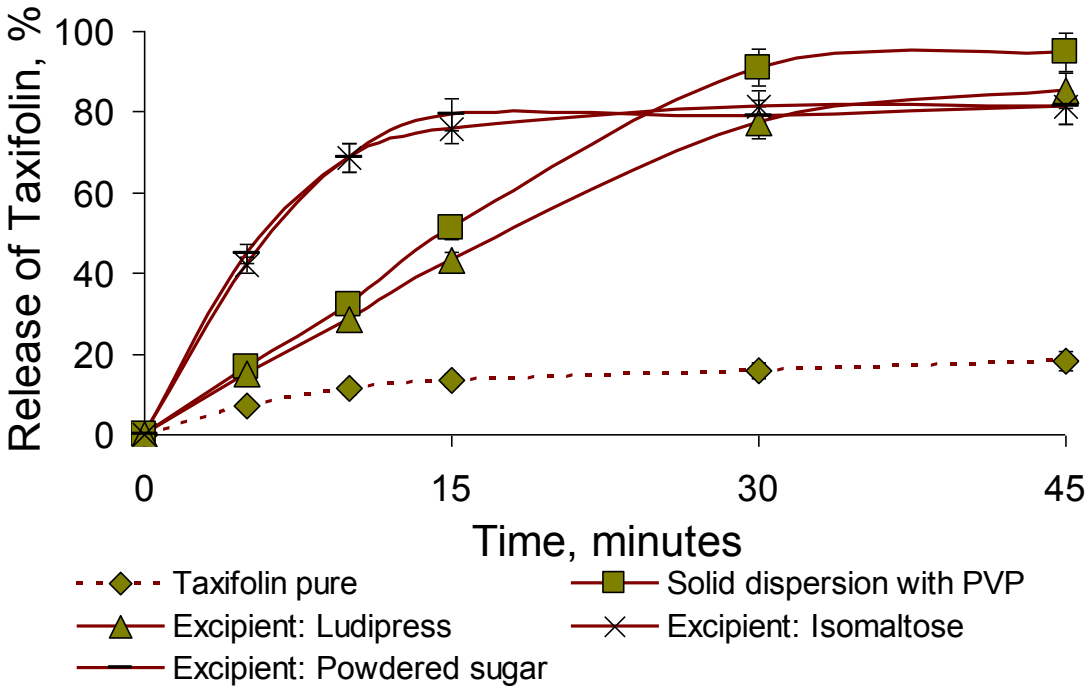
1. Amorphous formulations: Solid dispersion





In vitro testing:

1. Amorphous formulations: Solid dispersion

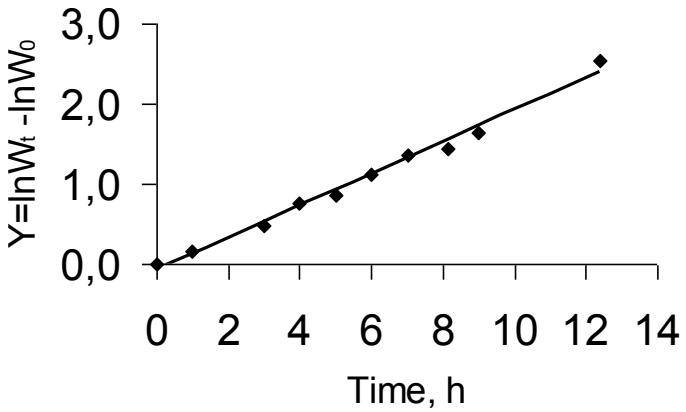


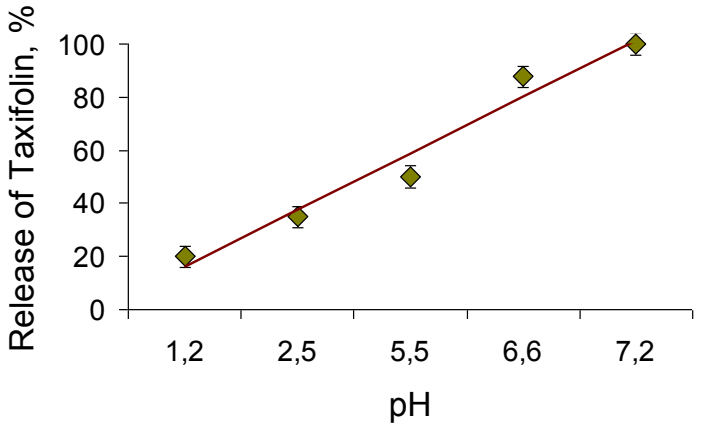
Taxifolin release from **Fast tablets** on the base of solid dispersions

In vitro testing:
1. Amorphous formulations

- Basket method, USP dissolution apparatus 1
- Dissolution medium: water

Modelling of transit of extended-release matrices through a gastroenteric path

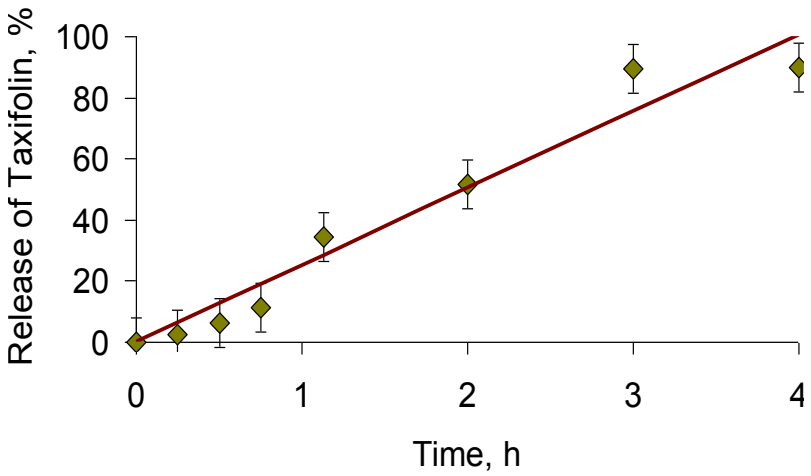




Taxifolin release from **Retard tablets** on the base of solid dispersions

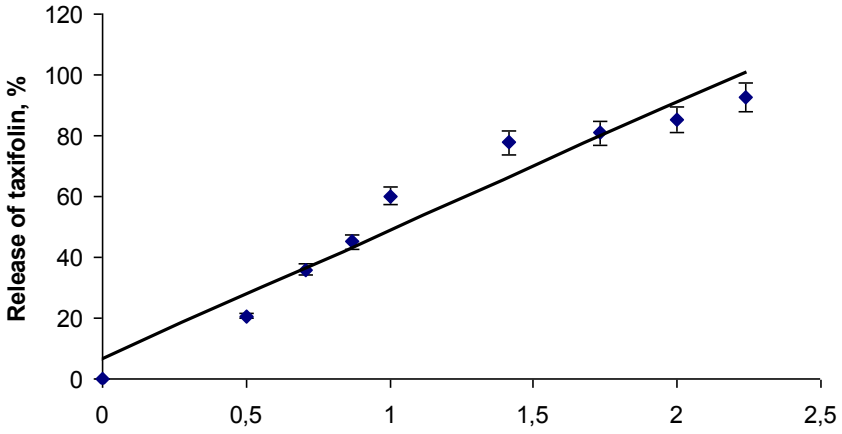
In vitro testing
2. Lipid formulations

Taxifolin release from **SMEDDS** at modeling of oral application



- The constants of rate release 0,8476 h^{-1}[c]

Taxifolin release from **oil solution** at modeling of oral

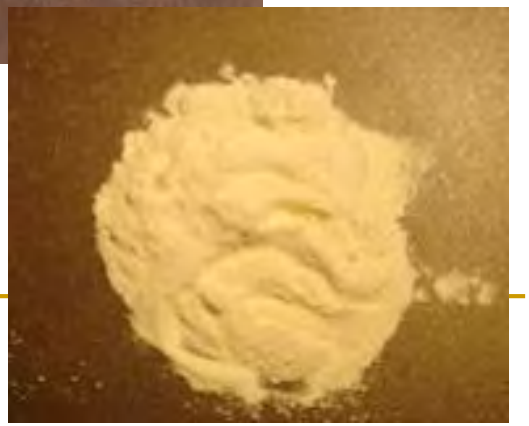


- The constants of rate release 0,3948 h^{-1}

Non-conventional dissolution test; Paddle method, USP dissolution apparatus 2. Dissolution medium: *n*-octanol:water 1:3. Temperature 37±0.5 °C; Rotation speed 100 rpm

Design of dosage form of boswellia extract

- Standardized dry extract *Boswellia serrata* (total organic acids in equivalents of boswellic acid not less than 85 %)



Physic-chemical properties of ketoboswellic acids

Soluble:

- Poorly soluble in water
- Fairly soluble in methanol
- Soluble in chloroform

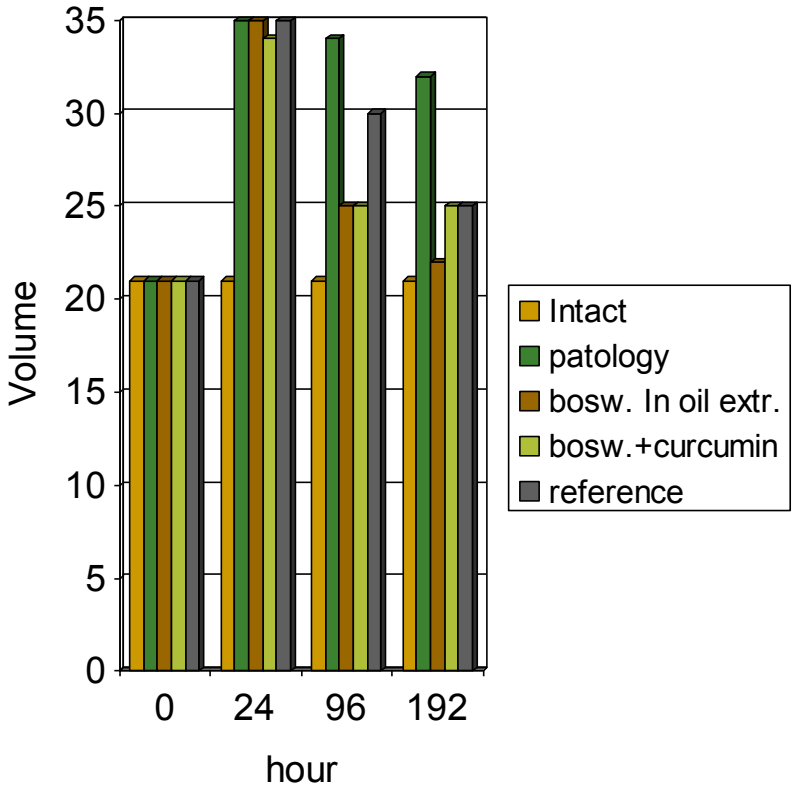
Theoretically calculated coefficient of distribution octanol-water (log P):

11-keto-β-boswellic acid – 7,10±0,39

3-o-acetyl-11-keto-β-boswellic acid – 8,00±0,28

Tests for biological activity

- Anti-inflammatory activity
  - model of formalin arthritis
  - administration 4 days prior to inflammation one time per day intragastrically, than for 7 days one time per day.



Rat paw volume

Design of dosage form of Boswellia extract

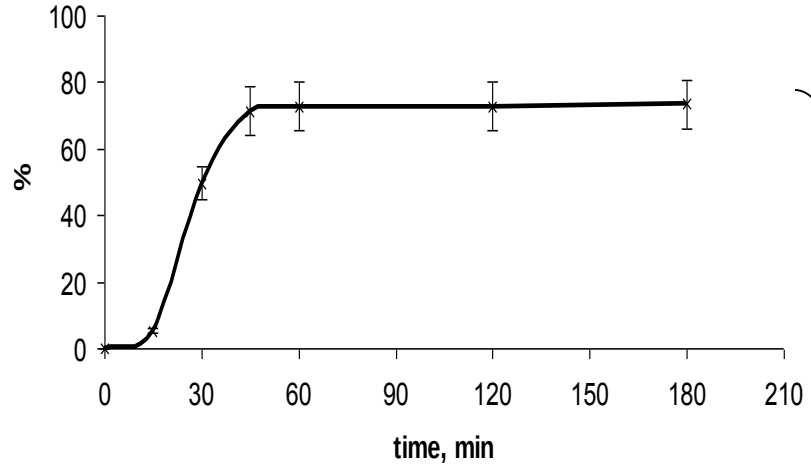
Lipid formulations

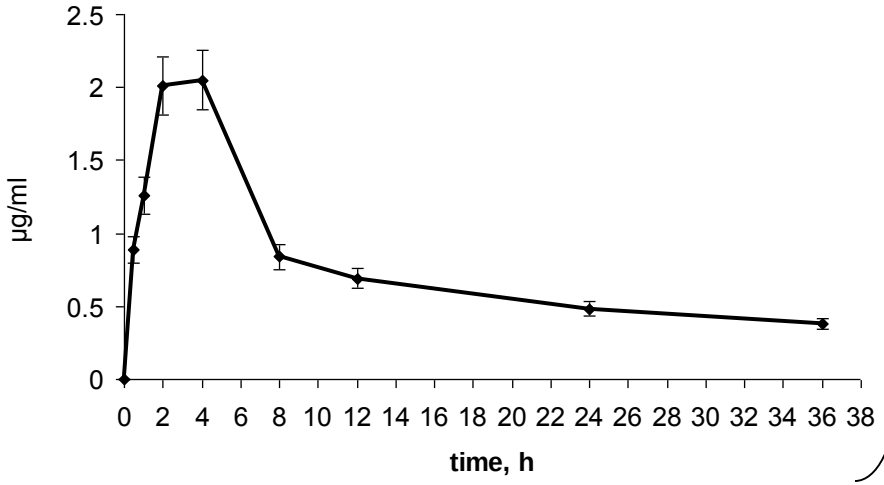
dry extract of Boswellia in oil extract of *Curcuma longa* and *Pinus sibirica*

Dosage form

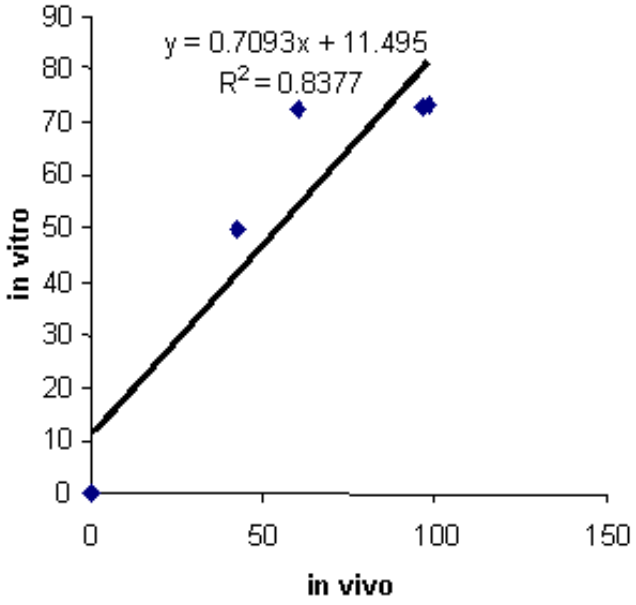
soft gelatin capsules 0.3 g

IVIVC for 3-o-acetyl-11-keto-β-boswellic acid





Ivivc levels A



Challenges in development of drugs

- Compound development of drugs discovered from medicinal plants also faces unique challenges.
  - Natural products are typically isolated in small quantities
  - that are insufficient for lead optimization, lead development, and clinical trials.
  - Collaborating with synthetic and medicinal chemists is necessary to determine if synthesis or semi-synthesis might be possible.
  - Another technique to improve natural product compound development may involve the creation of natural product and natural-product-like libraries that combine the features of natural products with combinatorial chemistry

Challenges in development of drugs

- Drug discovery from medicinal plants has traditionally been so time-consuming, faster and better methodologies for plant collection, bioassay screening, compound isolation, and compound development must be employed.
- Innovative strategies to improve the process of plant collection are needed.
- Redirecting plant collections may be one such strategy.

Challenges in development of drugs

- The design, determination, and realization of appropriate, clinically relevant, high-throughput bioassays is a difficult process for all drug discovery programs.
- Although the design of high-throughput screening assays can be challenging, after a screening assay is in place, compound and extract libraries can be tested for biological activity.
- Screening of extract libraries can be problematic, but new techniques, including prefractionation of extracts, can alleviate some of these issues.
- Challenges in bioassay screening remain an important issue in the future of drug discovery from medicinal plants.

In conclusion

- Natural products discovered from medicinal plants (and derivatives thereof) have provided numerous clinically used medicines.
- Even with all the challenges facing drug discovery from medicinal plants, natural products isolated from medicinal plants can be predicted to remain an essential component in the search for new medicines.

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Thank you for your attention