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Bioactive Molecules from Plants:
Extraction, Nanoencapsulation and Applications

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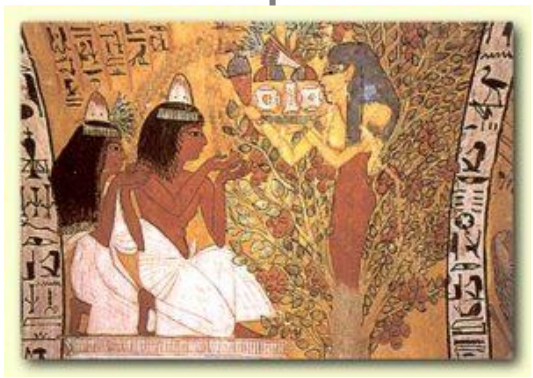
PLANTS AS SOURCE OF BIOACTIVE MOLECULES

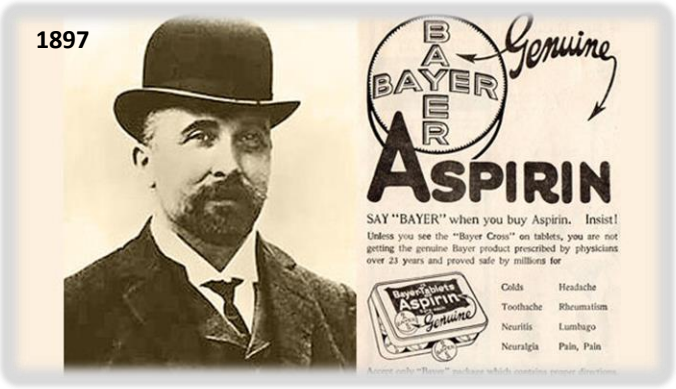
Plant-derived products have dominated the human pharmacopoeia for thousands of years ……..until the synthesis of aspirin ushered in an era dominated by the pharmaceutical industry

The history of drugs

60,000 years ago



1897



The Renaissance of Natural Products as Drug Candidates

Ian Paterson and Edward A. Anderson

Around half of the drugs currently in clinical use are of natural product origin (*1*, *2*). Despite this statistic, pharmaceutical companies have embraced the era of combinatorial chemistry, neglecting the development of natural products as potential drug candidates in favor of high-throughput synthesis of large compound libraries (*3*). Perhaps it is time to reassess this prevailing dogma for chasing quantity over quality.

Cancer chemotherapy, in particular, presents an ideal opportunity for natural product–inspired drug discovery and development. Unfortunately, many of the most promising natural lead compounds are available only in extremely small quantities, especially those from marine organisms such as sponges. The reluctance of industry to pursue such bioactive natural products as potential drugs lies primarily in the perceived supply problem. This leaves organic synthesis as a key option for sourcing these important drug candidates for preclinical and clinical studies. However, the academic-style approach to "hot target molecules" usually results in lengthy synthetic routes owing to their often exquisitely complicated architectures, with long development times, low overall yields, and impracticality of scale-up and provision of diverse structural analogs.

An alternative approach to drug discovery, which has been embraced by the phar-

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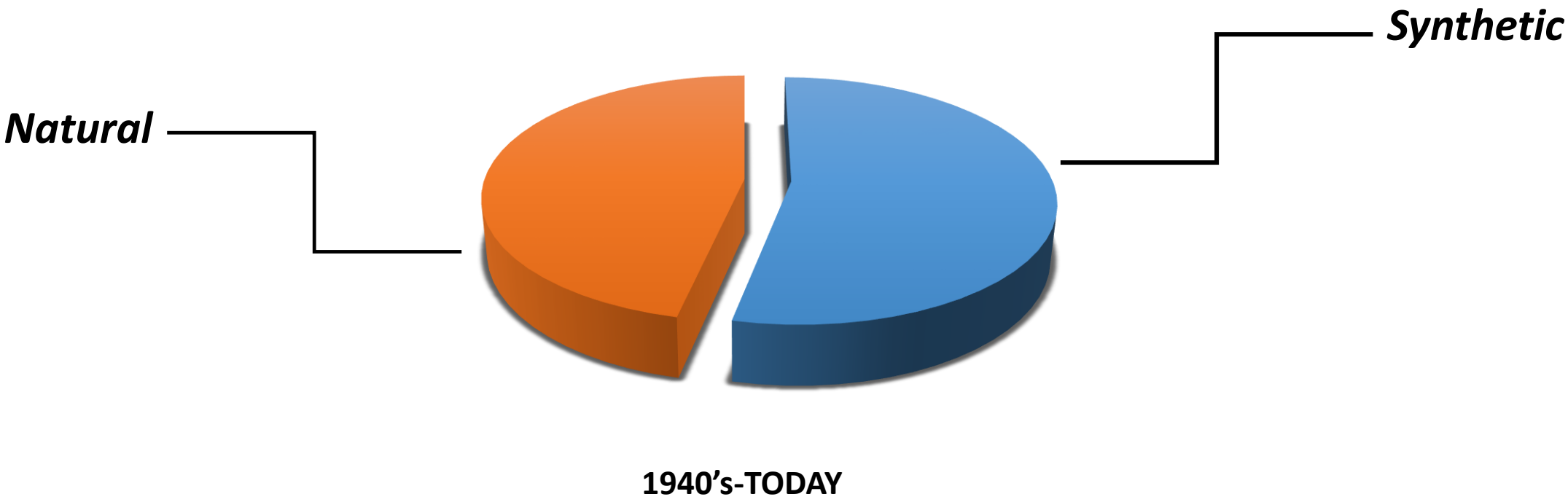
towards the scientific validation of medicinal plants from all over the world and the isolation of bioactive molecules from natural sources

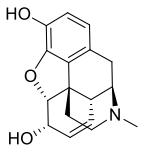


1940's-TODAY

CURRENT CATEGORIES OF BOTANICAL PRODUCTS

- ✓ **Nutraceuticals:** dietary components that are intended to supplement the diet

- ✓ **Drugs:** pure compounds isolated from plants and subjected to the **same rigors as synthetic pharmaceuticals**



- ✓ **Botanical Drugs:** complex extracts from a plant to be used for the treatment of disease

EXTRACTION OF BIOACTIVE COMPOUNDS FROM PLANTS

MAJOR ISSUE: LOW AMOUNTS OF METABOLITES IN PLANTS

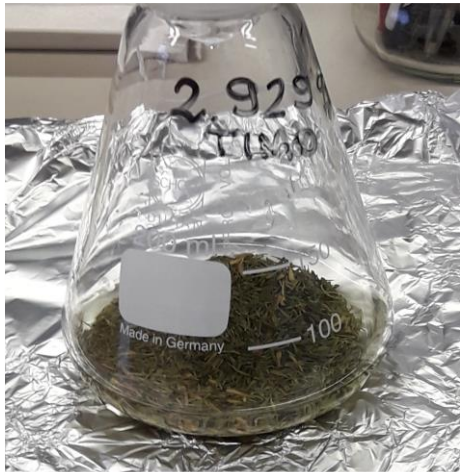
- ✓ lab-intensive procedures
- ✓ time-consuming procedures

Conventional methods: solvent extraction, distillation method, pressing and sublimation

👎 **Time**

👎 **Efficiency**

👍 **Stability**

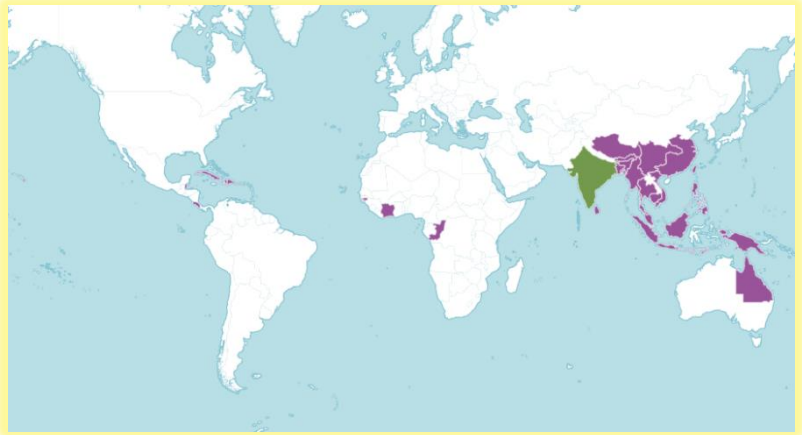


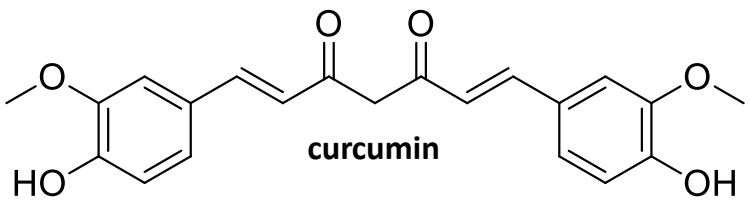
- Solvent extraction methods -

- Easiest and simple methods

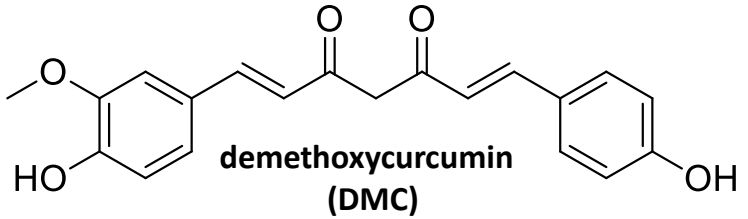
- **Large volume of solvents**
- Lower extraction efficiency
- Decomposition of thermolabile components

EXTRACTION OF BIOACTIVE COMPOUNDS FROM PLANTS
The case of Curcuma longa L.

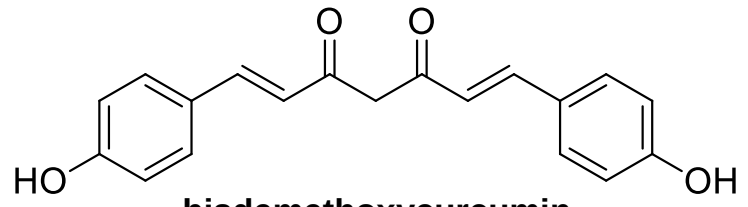




curcumin



demethoxycurcumin
(DMC)



bisdemethoxycurcumin
(BDMC)

Rhizome contents: curcuminoids (2–6%), volatile oil (3–7%), fiber (2–7%), mineral matter (3–7%), protein (6–8%), fat (5–10%), moisture (6–13%), and carbohydrate (60–70%)

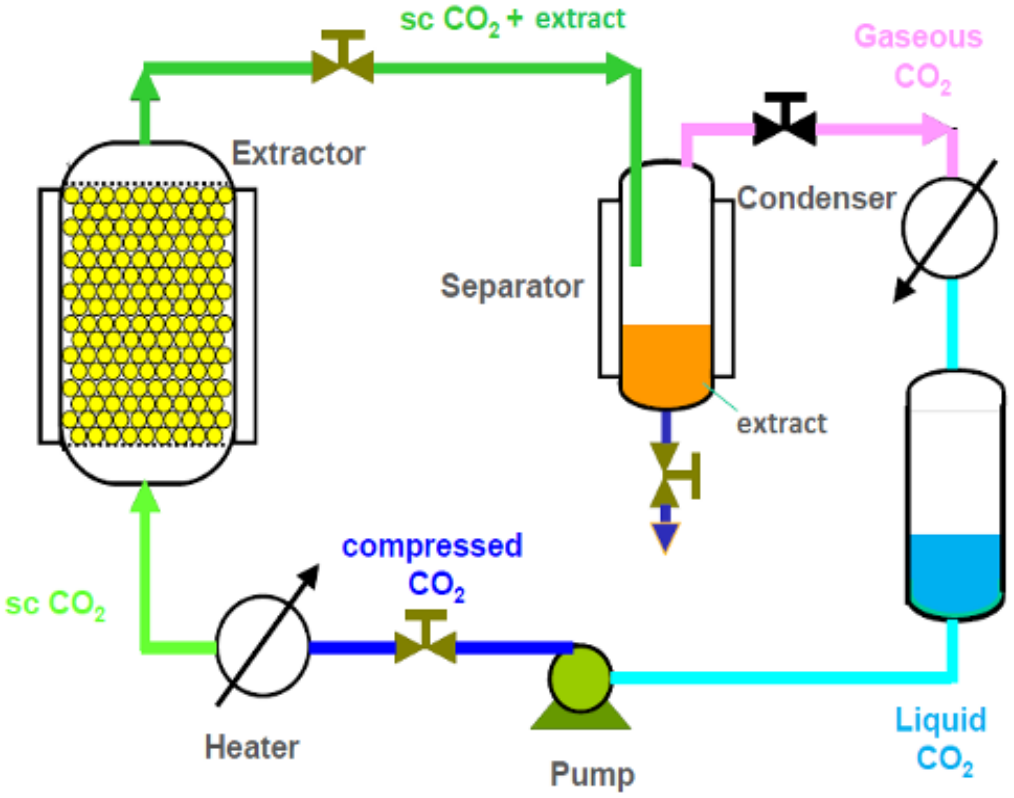
FROM CONVENTIONAL METHODS……

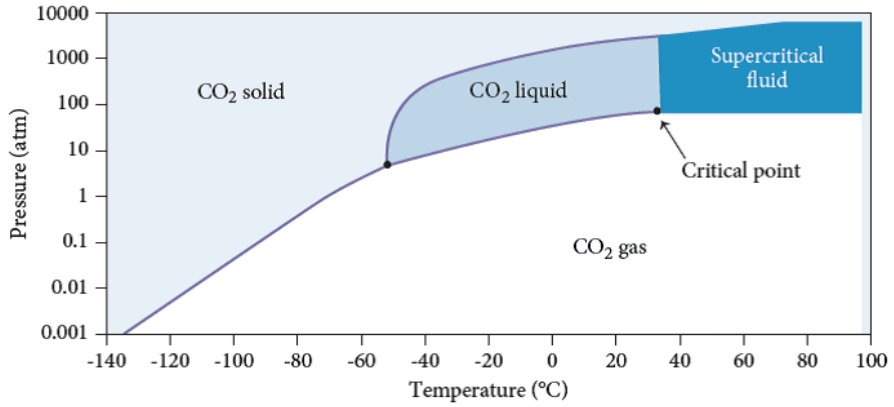
Ethanol: highest yield of extract, very low content in curcuminoids
Acetone/ethyl acetate: more appropriate, but more toxic!

……TO THE INNONATIVE ONES

- Microwaves assisted-extraction (**MAE**)
- Ultrasound assisted-extraction (**UAE**)
- Pulsed electric field (**PEF**) extraction
- **Ionic liquid-assisted extraction** (**ILAE**)
- **Supercritical fluid extraction** (**SFE**)

Supercritical fluid extraction (SFE) of *C. longa* L.





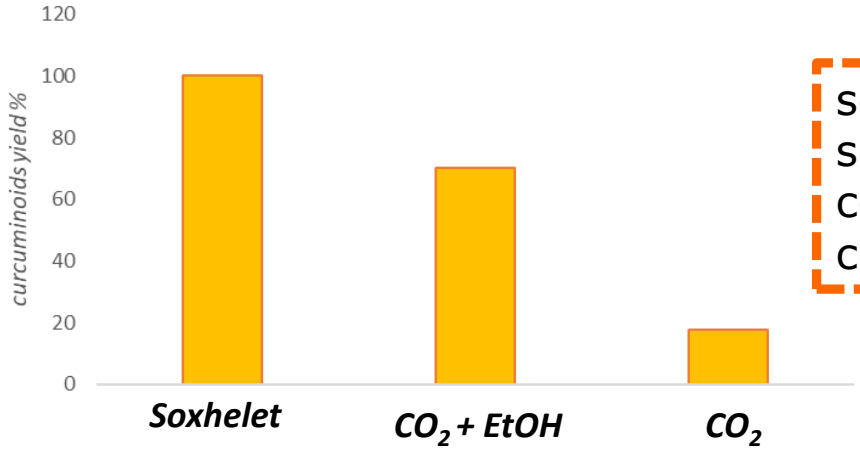
CO_2

- ✓ inexpensive, environmentally friendly and generally recognized as safe
- ✓ easily tunable solvent strength
- ✓ gaseous at room temperature and pressure, which makes extract recovery very simple and **provides solvent-free extracts**.

SFE-CO_2

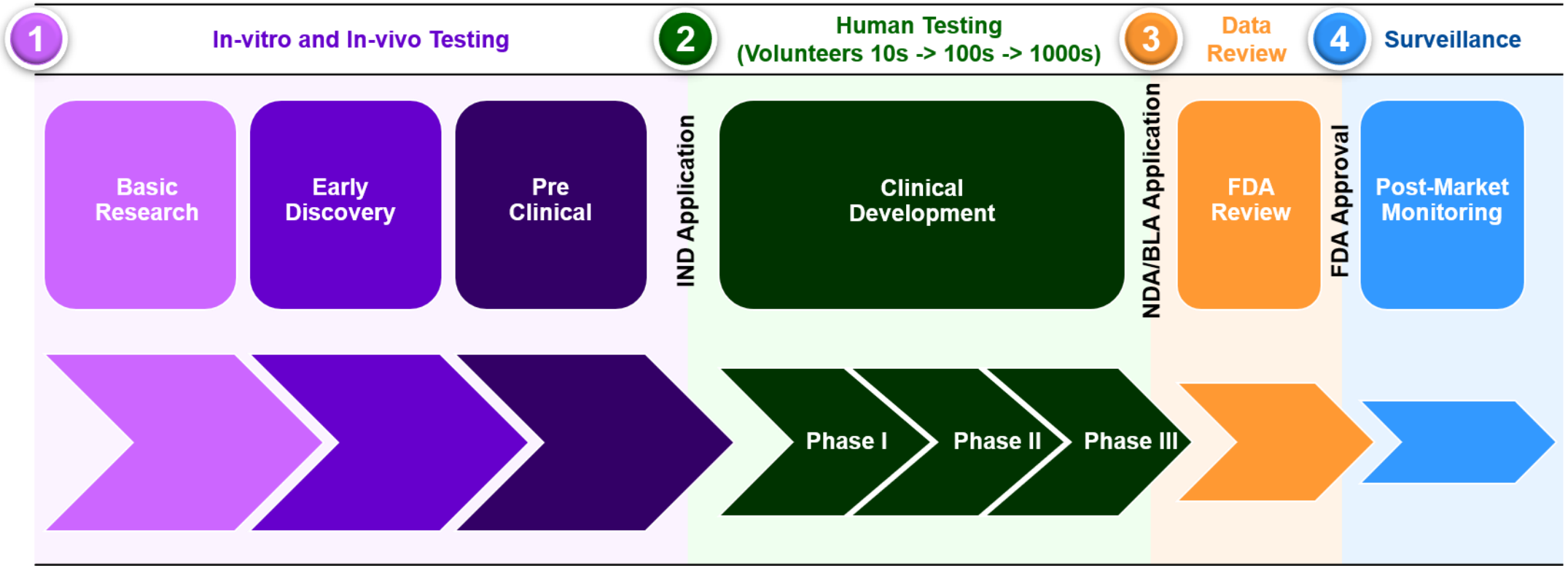
350 bar
65°C


Oleoresin of *C. longa*



scCO$_2$ + 30% EtOH s sufficient to achieve convincible amount of curcumin yield

DRUG DISCOVERY PROCESS



AFTER ISOLATION OF METABOLITES FROM PLANTS, THE EVALUATION OF THE BIOLOGICAL ACTIVITY CAN BE PERFORMED

From basic research to the market?

Some natural compounds failed at the preclinical phase

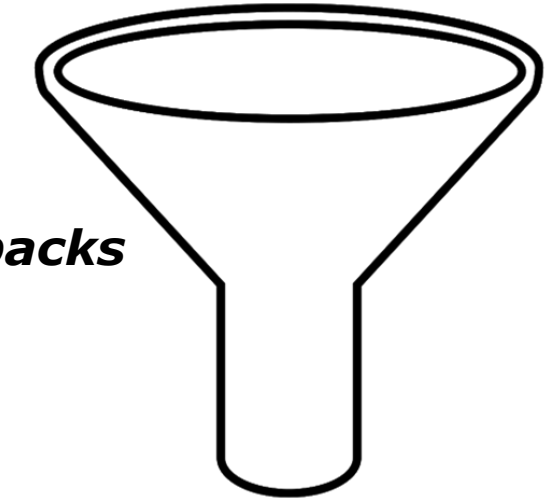
DRUG DISCOVERY AND NATURAL PRODUCTS
What challenges





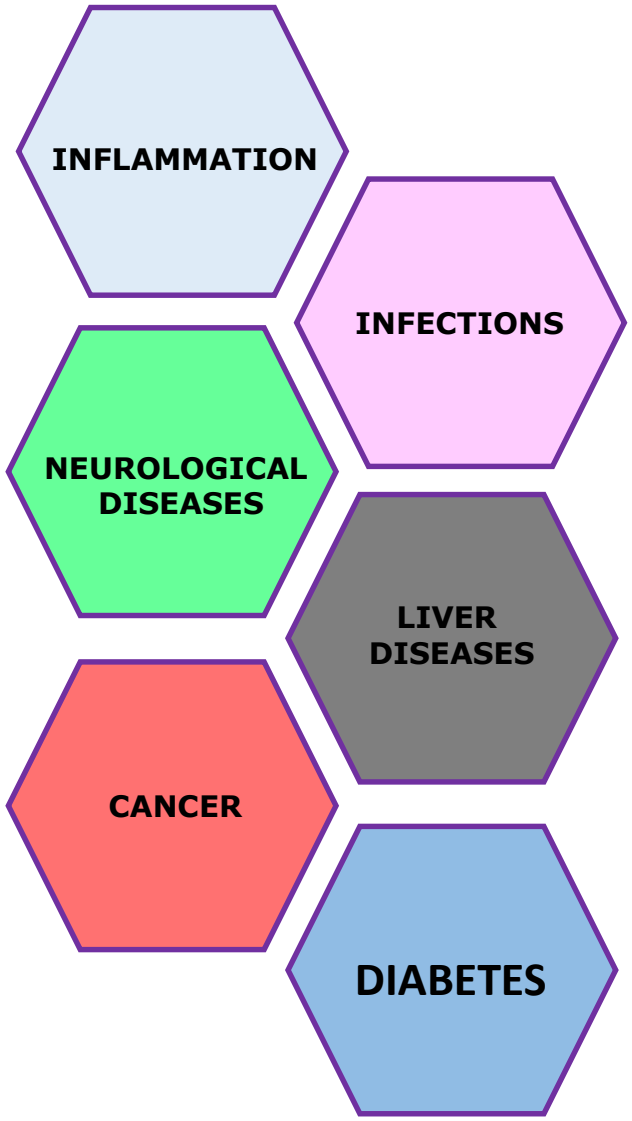
Major drawbacks

- ✓ Solubility
- ✓ Stability
- ✓ Selectivity



NANOTECHONOLOGY CAN HELP IN

- Improving **solubility**
- Improving **stability**
- Improving the **bioavailability** and effects of NP
- Reducing the toxicity by loading them into different types of delivery systems

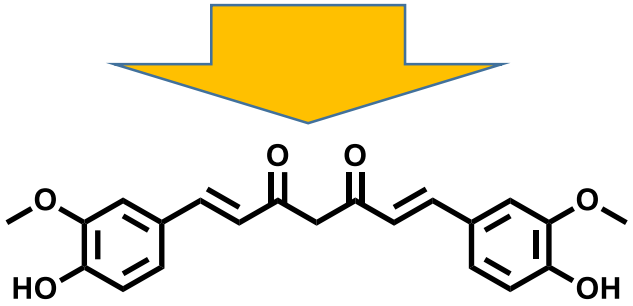


WIDE RANGE OF IN VITRO BIOLOGICAL ACITVITY

LOW BIOAVAILABILITY CAUSED PROBLEMS IN CLINICAL TRIALS

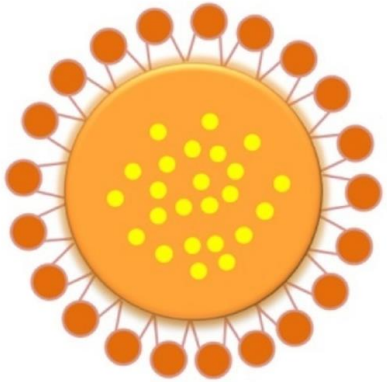
Curcumin orally required doses of 3.6 g/day to obtain serum levels of 11.1 nmol/L

One animal study found that when 1 g/kg of curcumin was orally administered, 75% of the compound was excreted through the feces

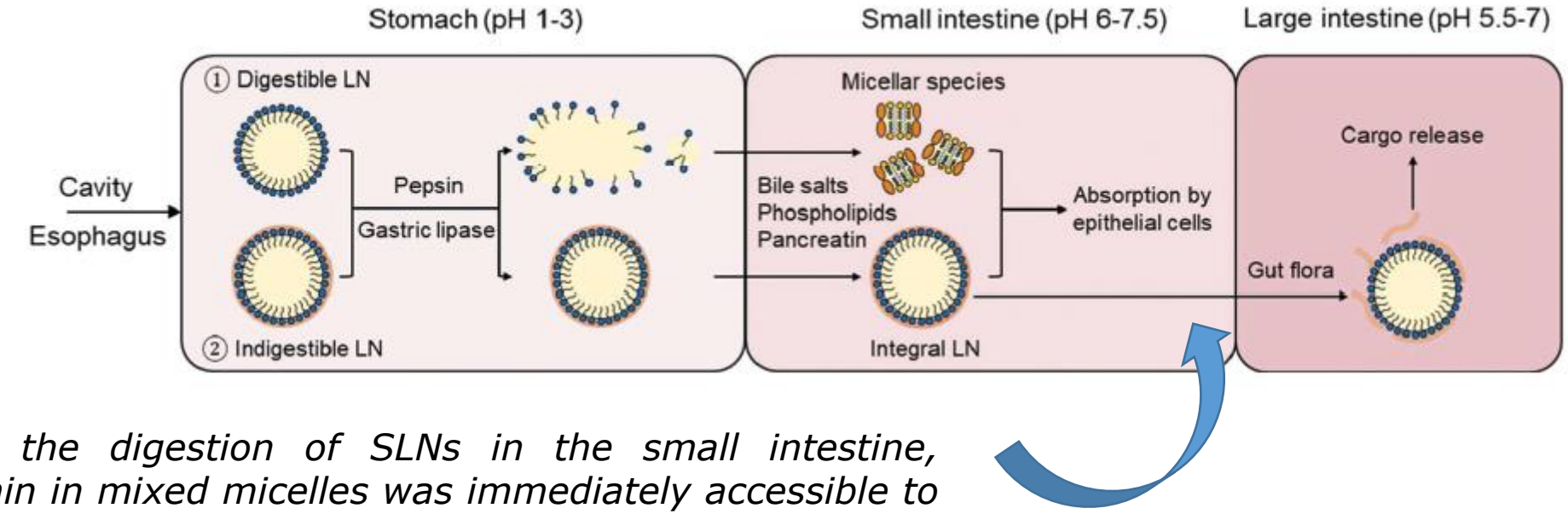


****poor absorption (→ low solubility) and high rate of metabolism****

SOLID LIPID NANOPARTICLES TO ENHANCE THE ORAL BIOAVAILABILITY OF CURCUMIN

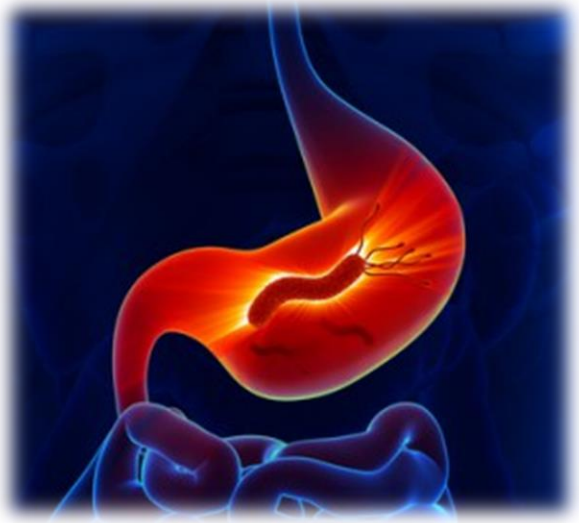


- **Lipid**: Tristearin
- **Emulsifier**: Polyethylene glycol (PEG)ylated
- **Entrapment efficiency** > 91%
- **>12.0–fold increase in bioavailability** compared to curcumin solution in a rat model

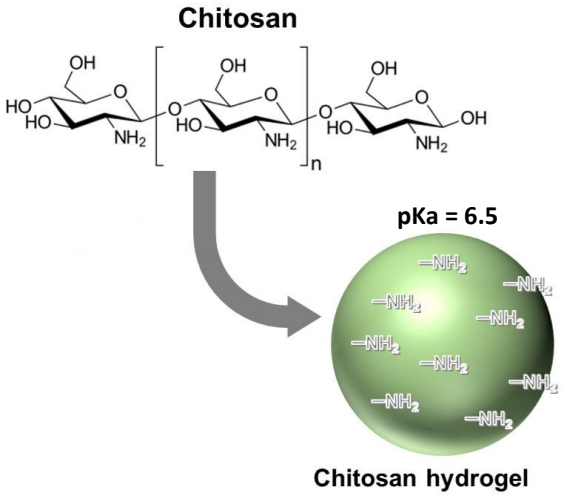


During the digestion of SLNs in the small intestine, curcumin in mixed micelles was immediately accessible to pass through the gut epithelium

NANOCELLULOSE REINFORCED CHITOSAN HYDROGELS



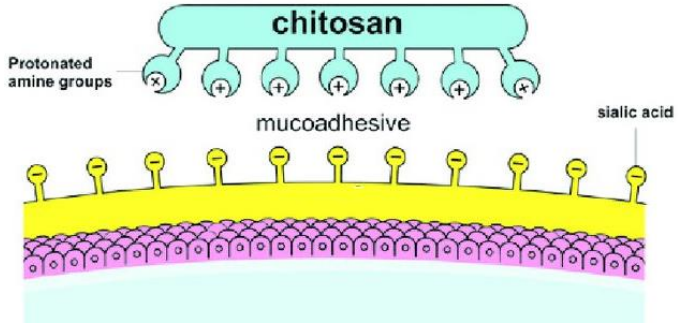
curcumin can block ethanol, indomethacin, stress-induced gastric ulcer and **can prevent pylorus-ligation-induced acid secretion**



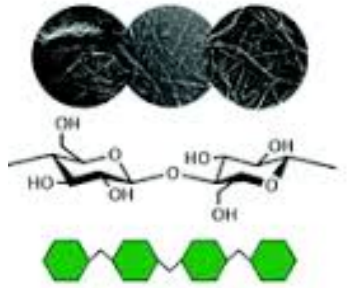
Hydrogel: highly swollen, hydrophilic, 3D polymeric networks capable of absorbing large amounts of water

Chitosan: highly swellable, pH responsive and biocompatible polymer

How improve the gastric residence time?



How improve mechanical strength and stability of hydrogels?



CONCLUSIONS

Bioactive compounds of plant origin possess desired health/wellness benefit effects in humans

Continuously growing interest in natural compounds has led to the development of innovative extraction techniques, more sustainable and **eco-friendly** allowing **higher yields in a shorter time**, significant reduction in solvent consumption and energy consumption

To **overcome phytochemical drawbacks** (instability, low solubility and poor absorption) **nanoencapsulation**, using biodegradable and biocompatible material, is a way to formulate them in order to enhance the therapeutic efficacy

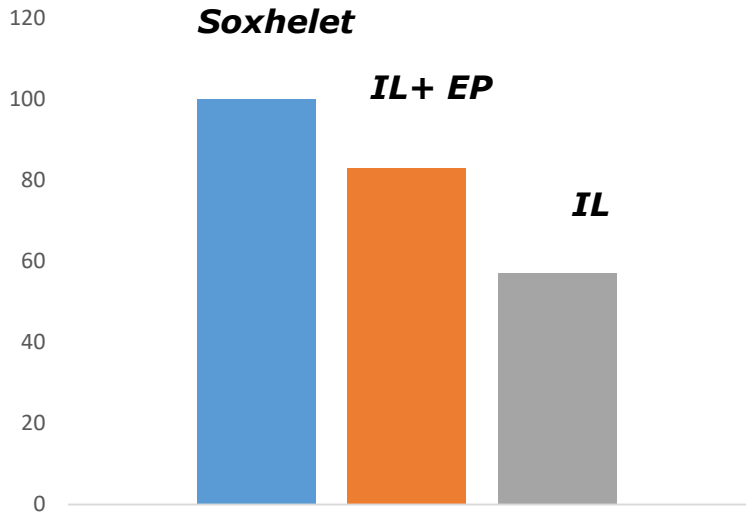

THANK YOU
FOR YOUR ATTENTION

Ionic liquid-assisted extraction (ILAE) of *C. longa* L.

- Liquid at RT
- Neglibible volatility
- Thermal stability

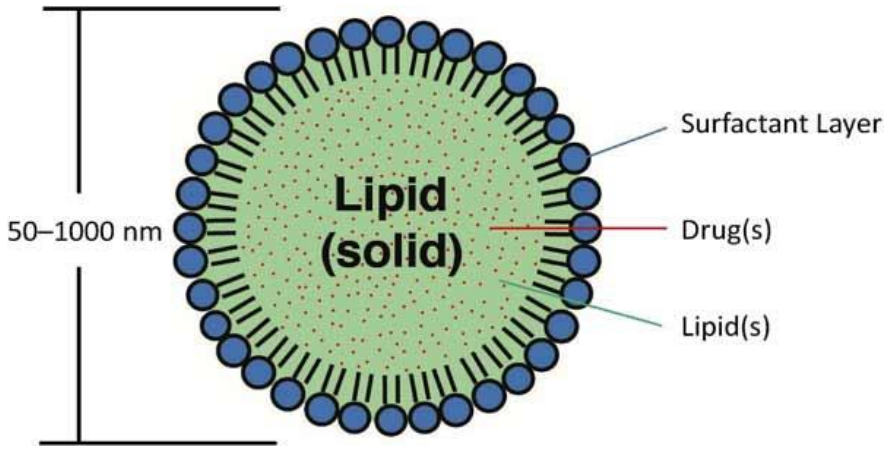
Turmeric (g)	IL (g)	oleoresin/turmeric (%)	curcumin/turmeric (%)
1	10	4.22	2.44
1	20	5.34	3.21
1	**30**	**5.81**	**3.48**
1	40	6.11	3.48
1	50	6.28	3.49

Constant yield
Waste of solvents

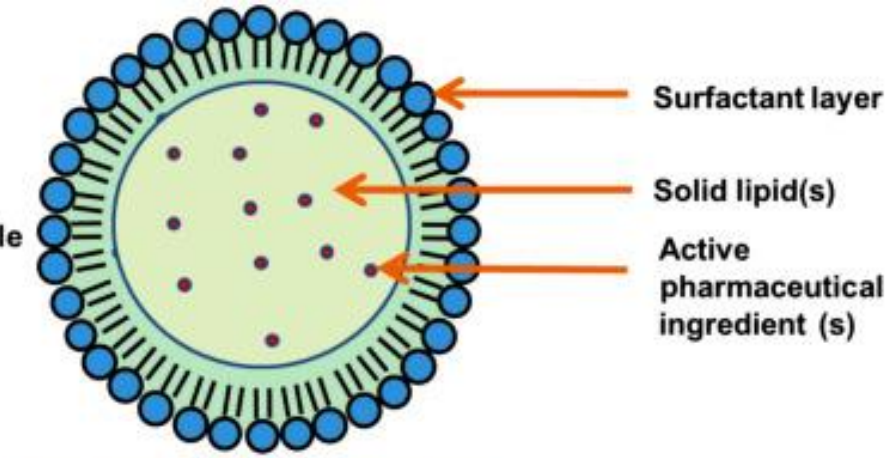


2 h extraction time at RT is sufficient to achieve convincible amount of curcumin yield

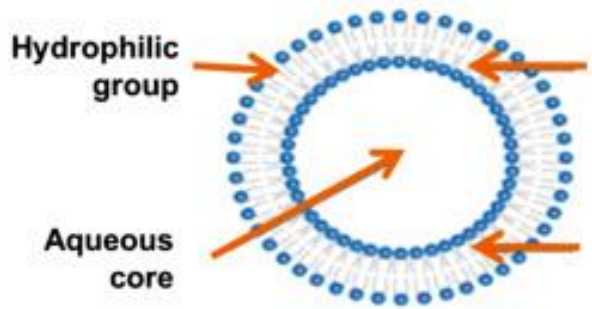
T (°C)	Time (h)	oleoresin/turmeric (%)	curcumin/turmeric (%)
15	1	4.06	2.47
25	1	4.72	2.77
35	1	3.97	2.16
45	1	3.86	1.98
15	2	4.87	3.17
25	**2**	**5.68**	**3.58**
35	2	4.70	2.92
45	2	4.01	2.11
15	4	5.70	3.67
25	4	5.79	3.72
25	12	6.21	3.93
25	24	6.24	3.95



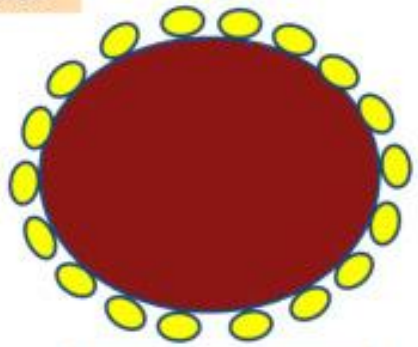
- ✓ Controlled drug release
- ✓ Drug targeting
- ✓ Longer stability
- ✓ High drug loading
- ✓ Biocompatible/biodegradable
- ✓ Nontoxic
- ✓ Ease of scale-up
- ✓ Efficient gene delivery



Solid lipid nanoparticles



Liposome



Lipid emulsion