TRANSLATIONAL SCIENCE IN DRUG DEVELOPMENT

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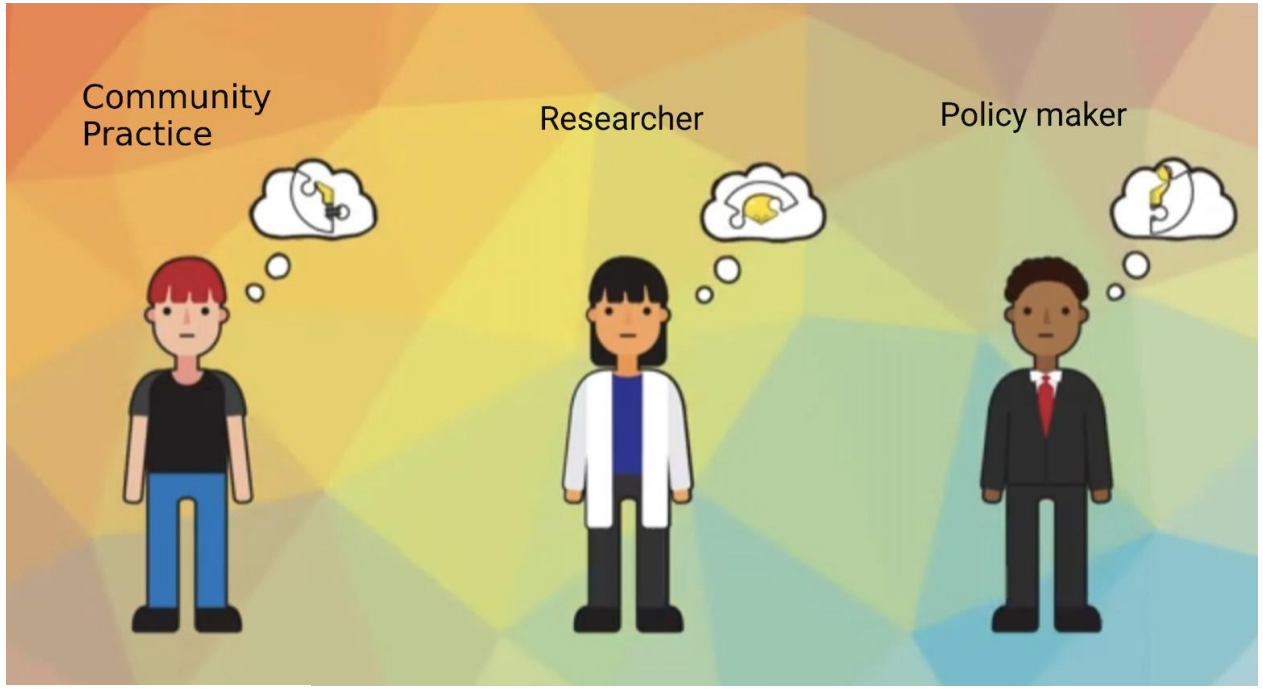
MALAYSIA

Acceleration in drug development

POLICY MAKER

Who involve?



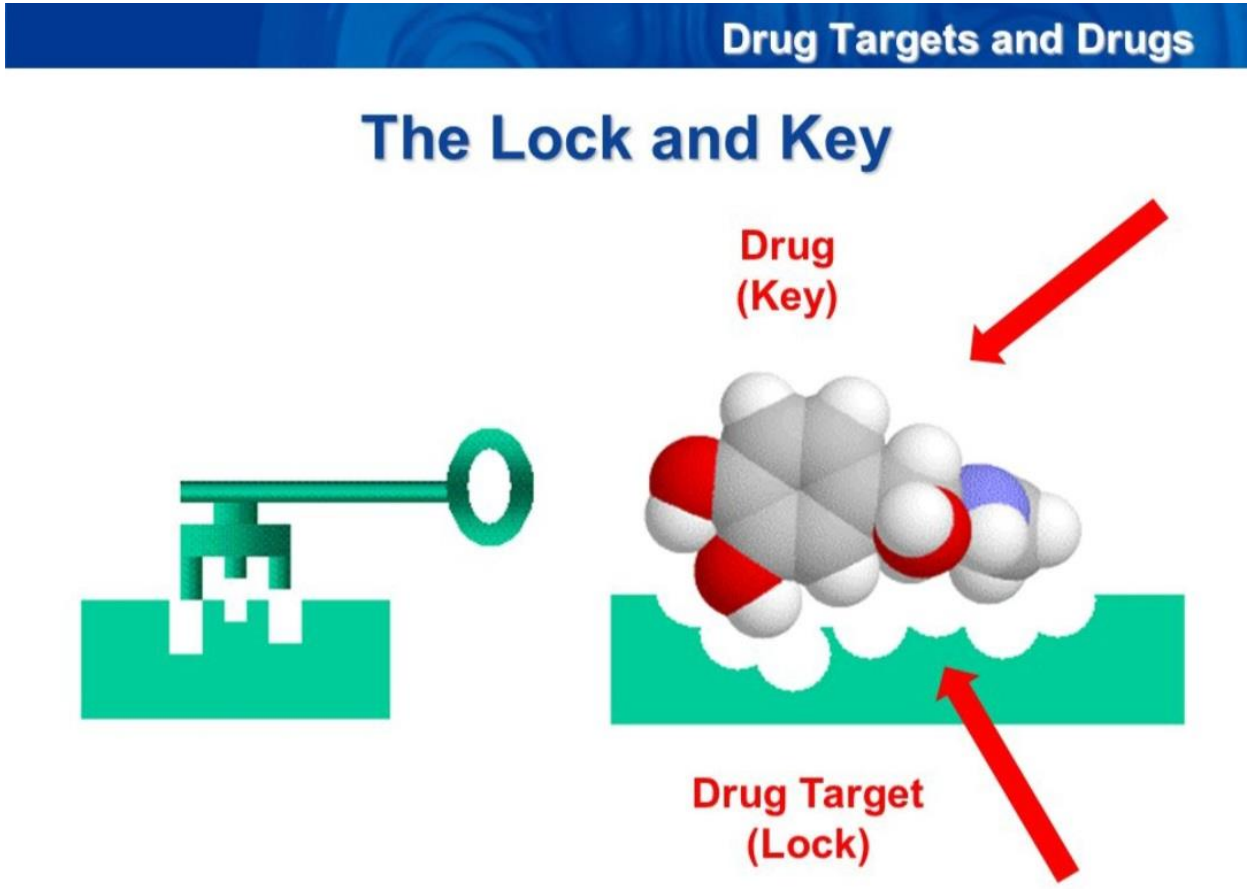
Basic research exploration

Traditional uses

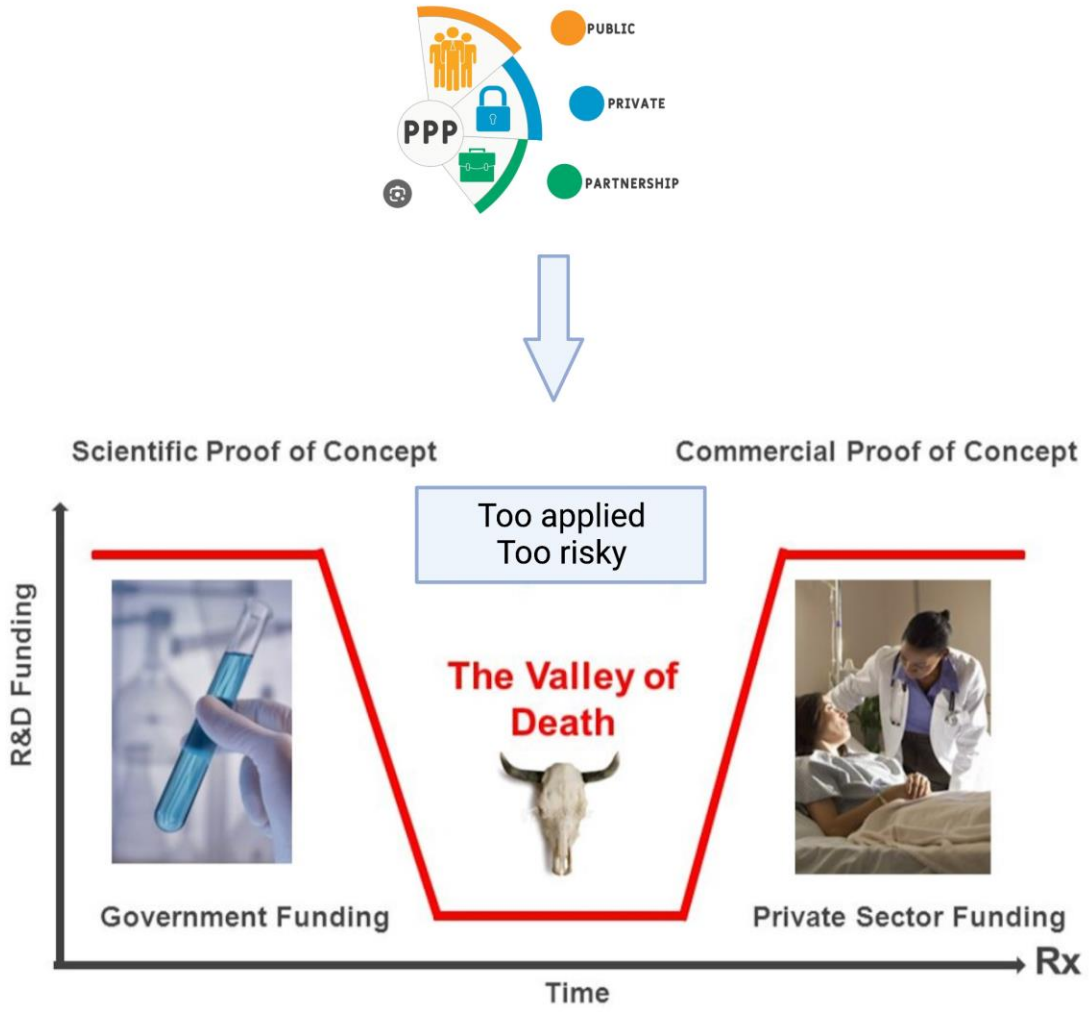
Holy book/ Old manuscript

How it works


Translational Research Defined by the Clinical Problem
Breast Cancer
Solution
Clinical Trials
Clinical Problem
Drug Treatment
Laboratory Research


Drug Targets and Drugs
The Lock and Key
Drug (Key)
Drug Target (Lock)

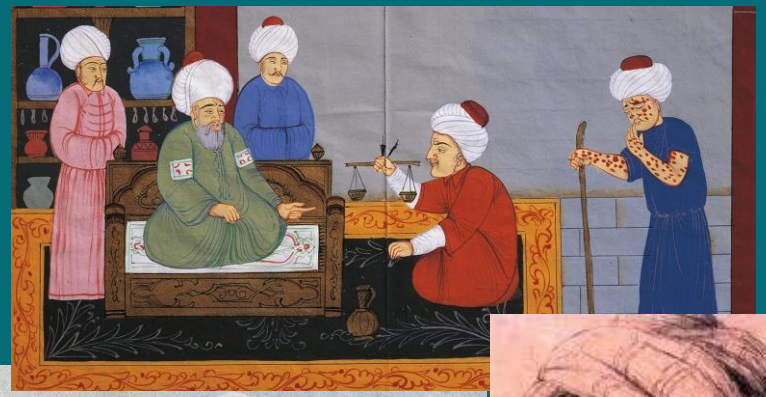
Lost in translation

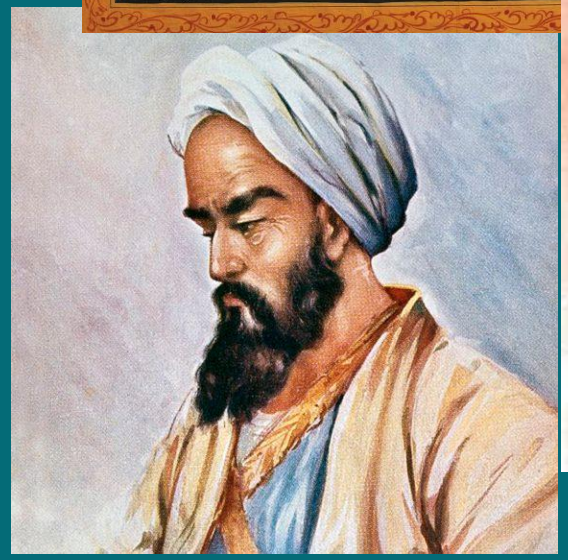


Medicinal plant heritages

- Kampo (Japanese Traditional Medicine)
- TCM (Traditional Chinese Medicine)
- Ayurveda (Traditional Indian Medicine)
- TAIM (Traditional Arabic and Islamic Medicine)
- Jamu (Indoesian Traditional Medicine)

TAIM (Traditional Arabic and Islamic Medicine)





Jabir ibn Hayyan (721 AD)
Founder of modern pharmacy

Ibn Sina (980 M)
Modern Physician

2400 B.C.; on clay tablets (Mesopotamia),
1534 B.C.; the Ebers Papyrus (9th year of Amenhotep 1 reign),
721 AD; Jabir ibn Hayyan, founder of modern pharmacy
980 AD; Ibn Sina, Modern Physician
1578 AD; the Chinese Materia Medica, document written by Li Shizhen in 1578 (Zheng 1988).
1804 AD; Serturner who dealt with medicinal herbs to the isolation of morphine

List of Islamic scholars in medicine

- Ali Al-Taberi (*Encyclopaedia medicine*)
- Al-Razi (Rhazes) (*Smallpox*)
- Ali Ibn Al-Abbas Al-Magusi (Haly) (*Complete Book of the Medical Art*)
- Ibn Al-Baitar (*Discovery cancer effects of the plant named "Hindiba*)
- Ibn Al-Qasim Al-Zahrawi (Abulcasis) (*Surgery)*
- Ibn Al-Haitham (Alhazen) (*The father of modern optics-Vision*)
- Ibn Abi Al-Zuhr (Avenzor) (*Anatomy*)
- Ibn Rushd (Averroes) (*Wrote 20 books on medicine*)
- Ibn Al-Nafis (*Pulmonary circulation*)

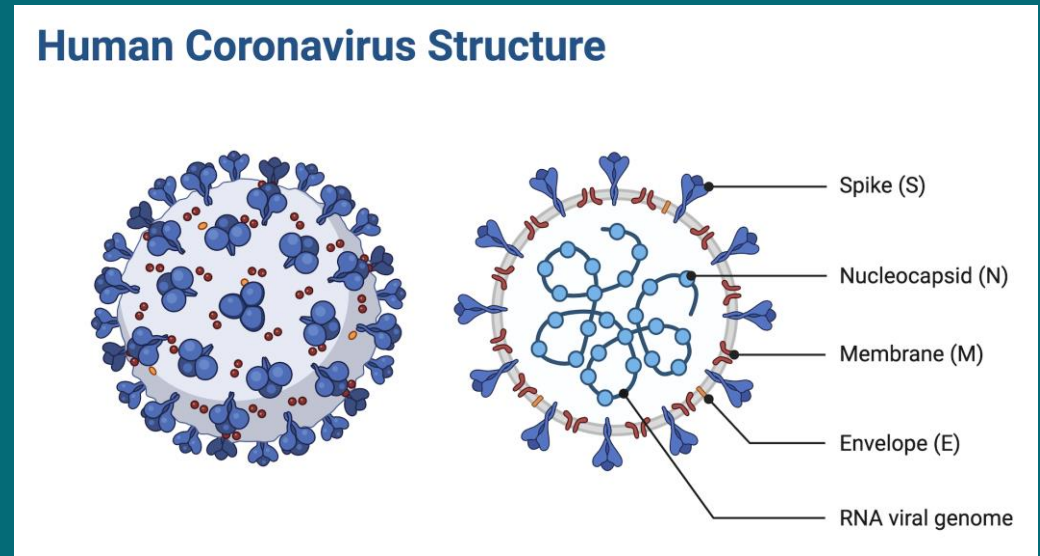
Maqasid al-Shariah (objective of Shariah)

Protecting life

ijtihad encourages the effort to research on drug, cosmetic and vaccines.

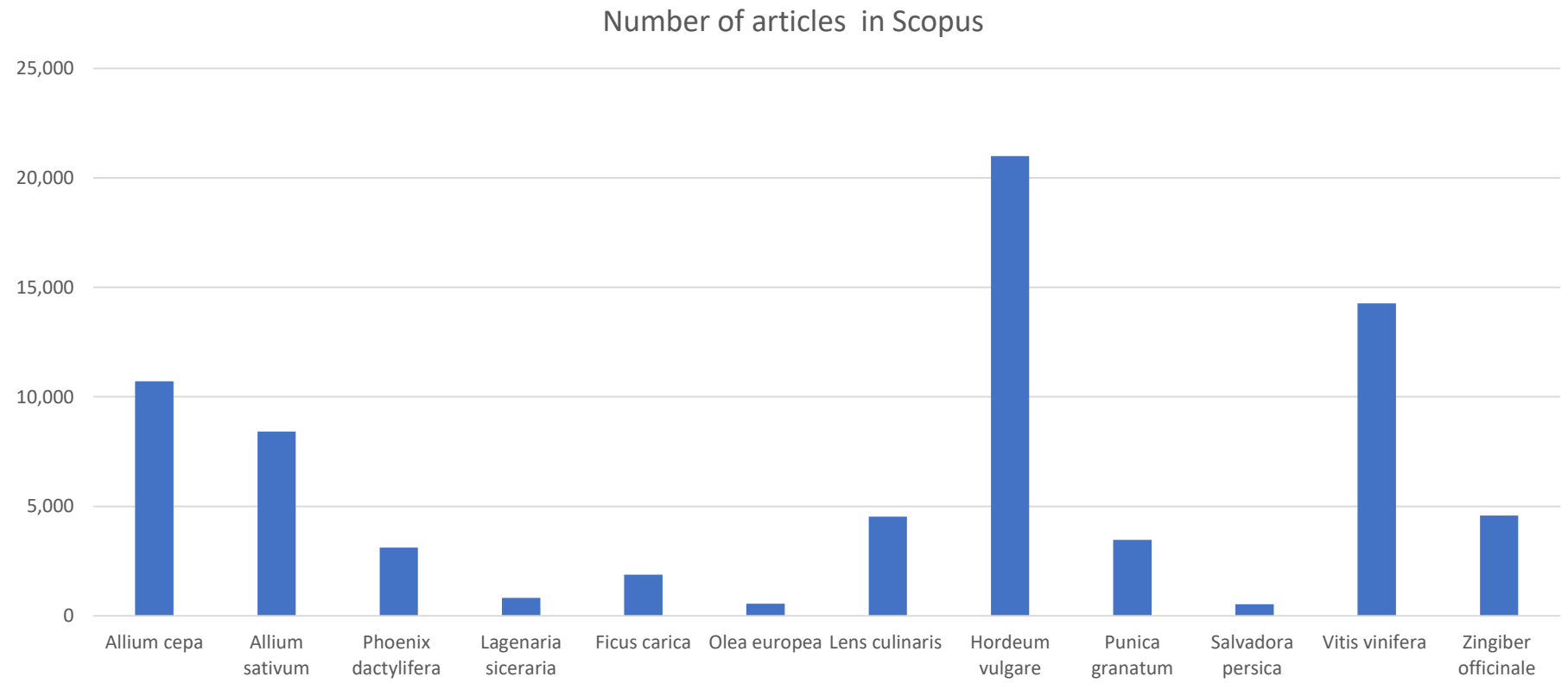
"*There is no disease that Allah has created, except that Allah also has created its cure*."

(Sahih Bukhari)



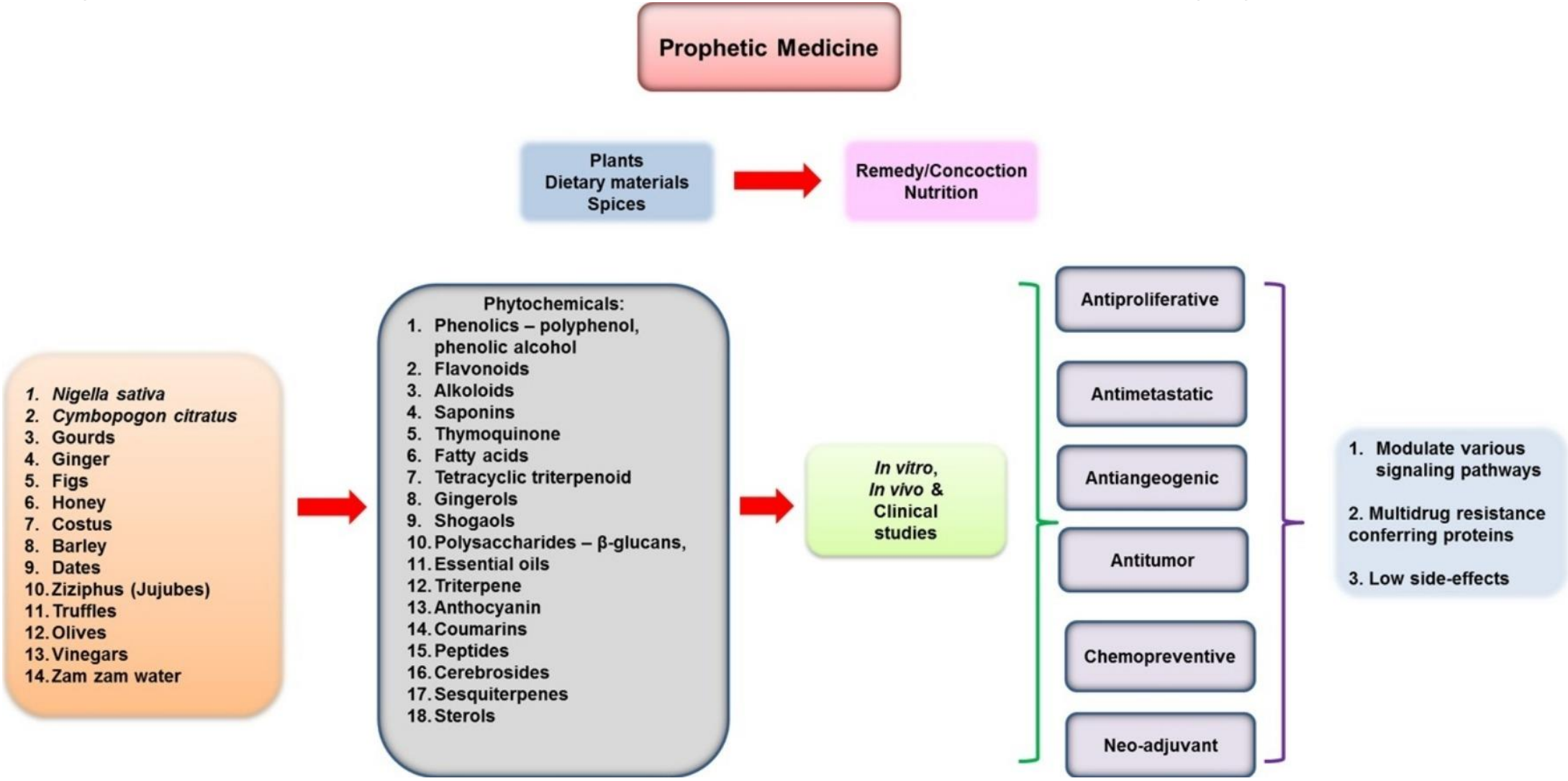
Natural Medicines According to Islamic Scriptures

Qur'anic plants
Prophetic plants



El-Seedi et 2019

Prophetic medicine in modern therapy

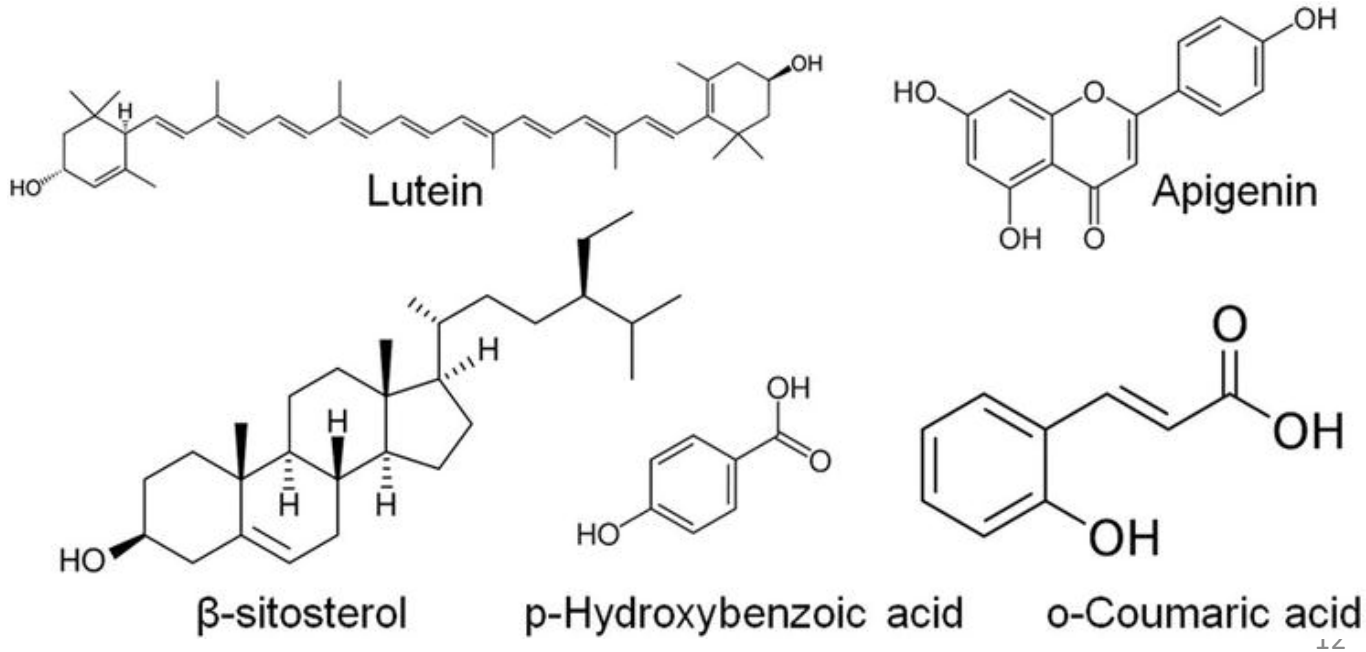


Source: Biomedicine & Pharmacotherapy Volume 95, November 2017, Pages 614-648

Dates palm (*Phoenix dactylifera* L.) fruits

According to Al-Bukhaari (5445) and Muslim (2047), narrated by Sa'd ibn Abi Waqqaas that the Prophet (PBUH) said: "Whoever eats seven Ajwa dates in the morning, will not be harmed by any poison or witchcraft that day."

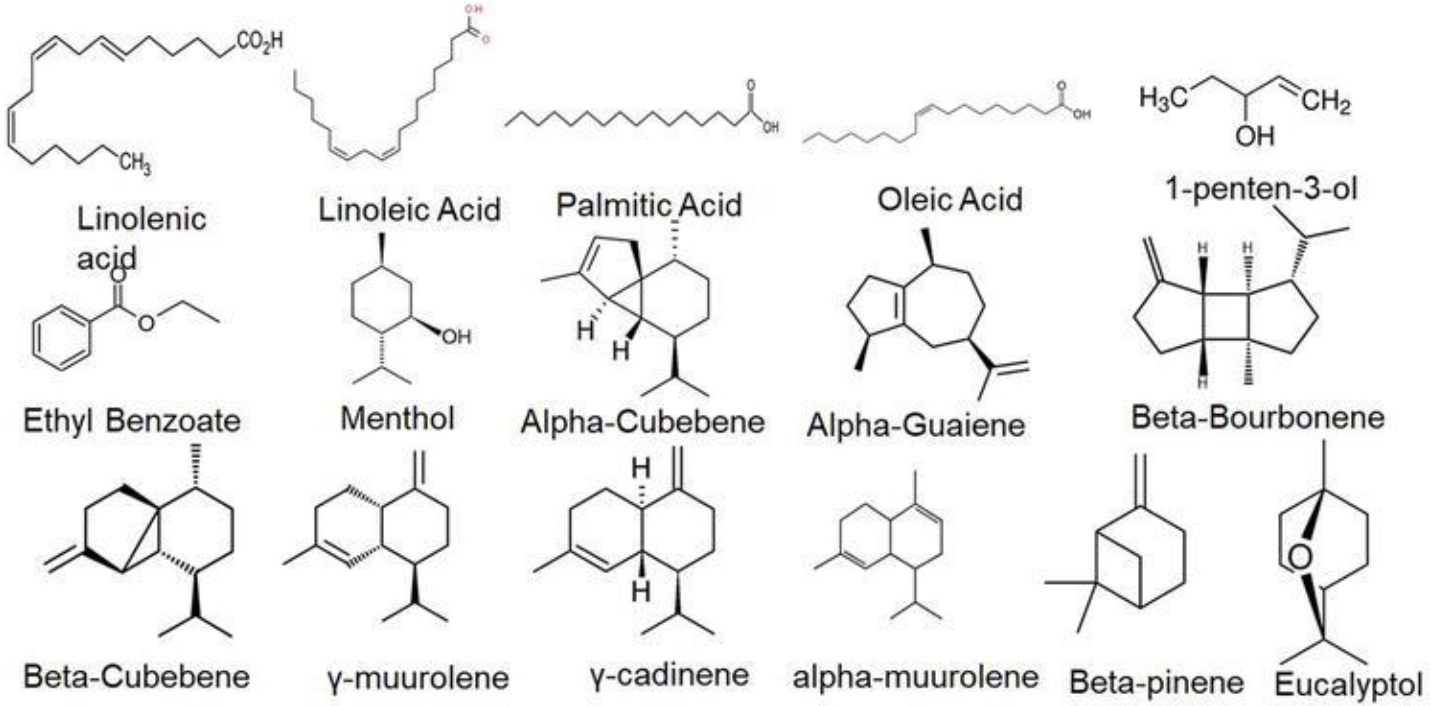
Anticholesteremic, antidiabetic, anti-inflammatory, antioxidant, hepatoprotective and anticancer effects



DOI: 10.5772/intechopen.101927

Fig (*Ficus carica*) fruit

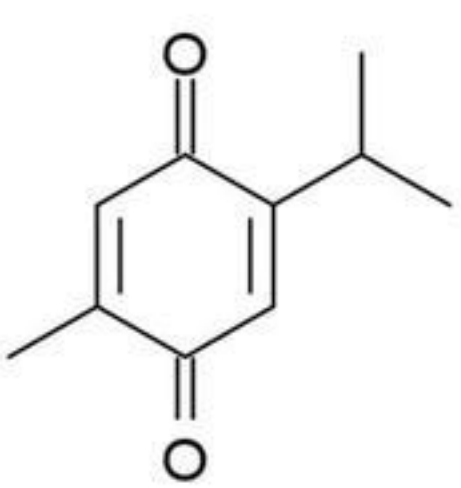
Ayurveda, Unani, and Siddha are the classical medicine systems of Ayurveda that have acknowledged the medicinal benefits of fig.
To treat and cure disorders of endocrine (diabetes), ventilatory, cardiovascular, digestive (ulcers and vomiting), urinary, reproductive (menstrual discomfort), and immune systems, as well as infectious diseases of the skin, scabies, and gonorrhea



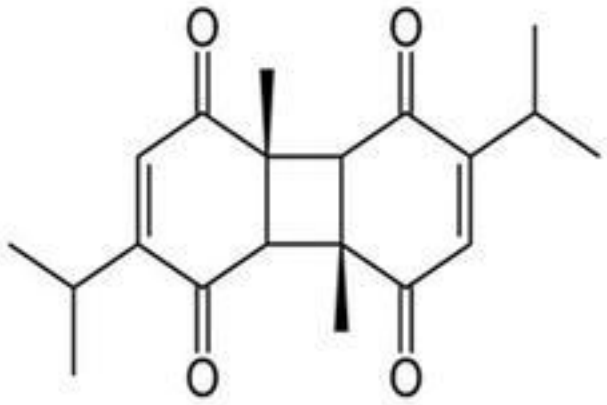
Black cumin/black seed/Nigella sativa

Rich historical and religious background

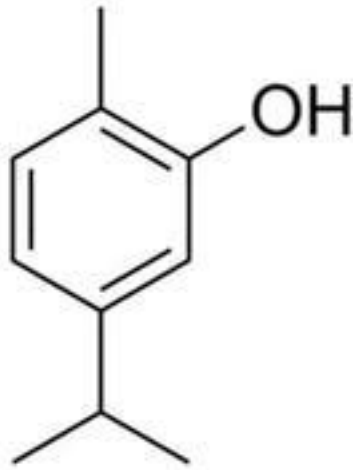
Traditional medicine for more than 2000 years; respiratory system, digestive tract, kidney and liver function, cardiovascular system, and immune system



Thymoquinone



Dithymoquinone



Carvacrol

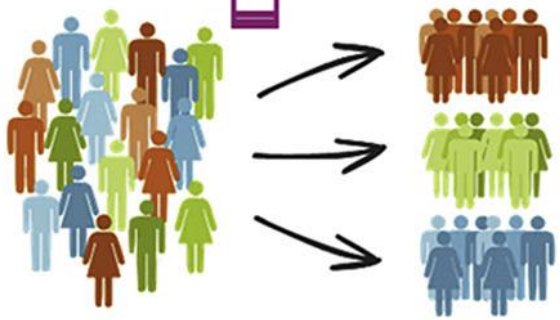
Translation of prophetic medicine

Drugs candidate for Anti-cancer, anti-oxidants, anti-microbial, anti-obesity and anti-emetic

Plants mentioned in Holy Qur'an Scriptures

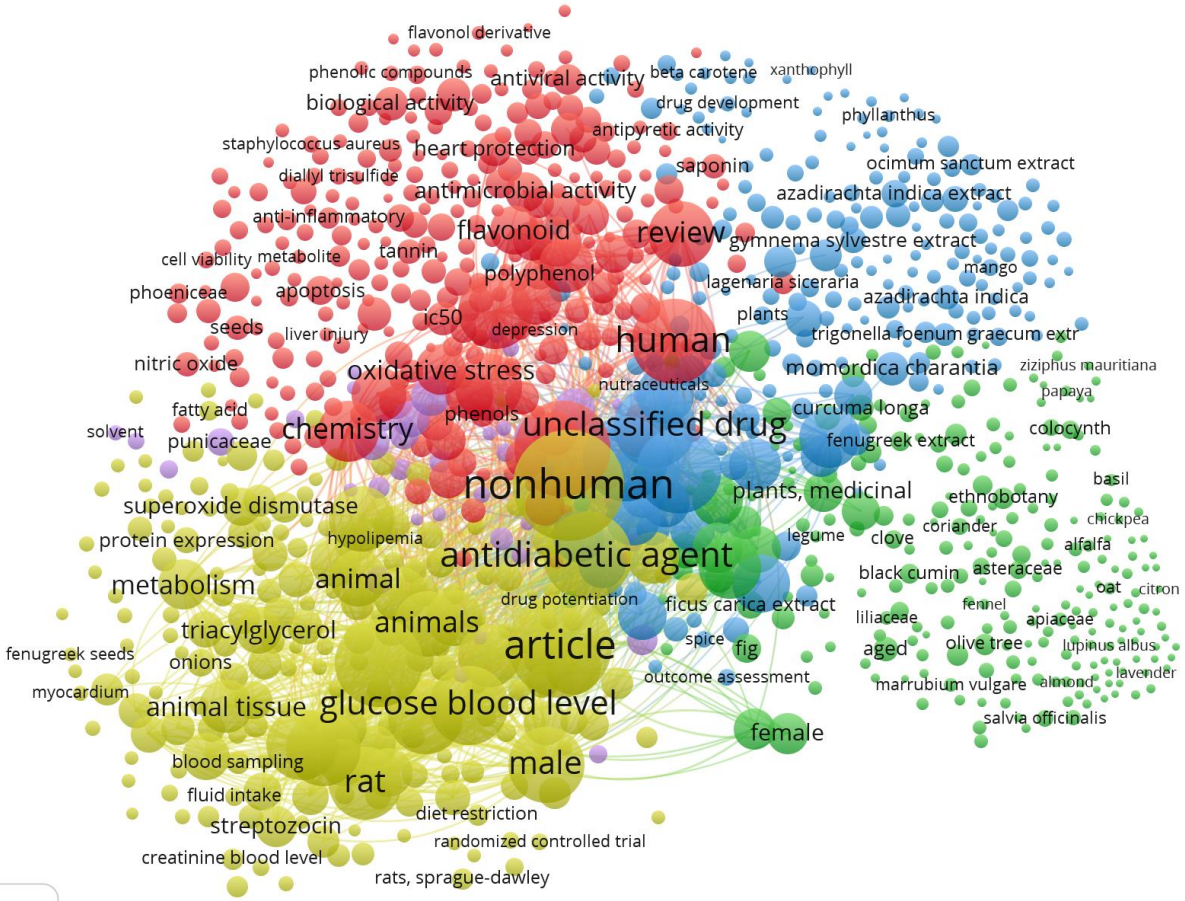
Traditional uses of the Holy plants by Islamic/ Greek/ Roman/ Persian/ Chinese/ Indian practitioners

Detection and investigation of biological activities (preclinical trials)

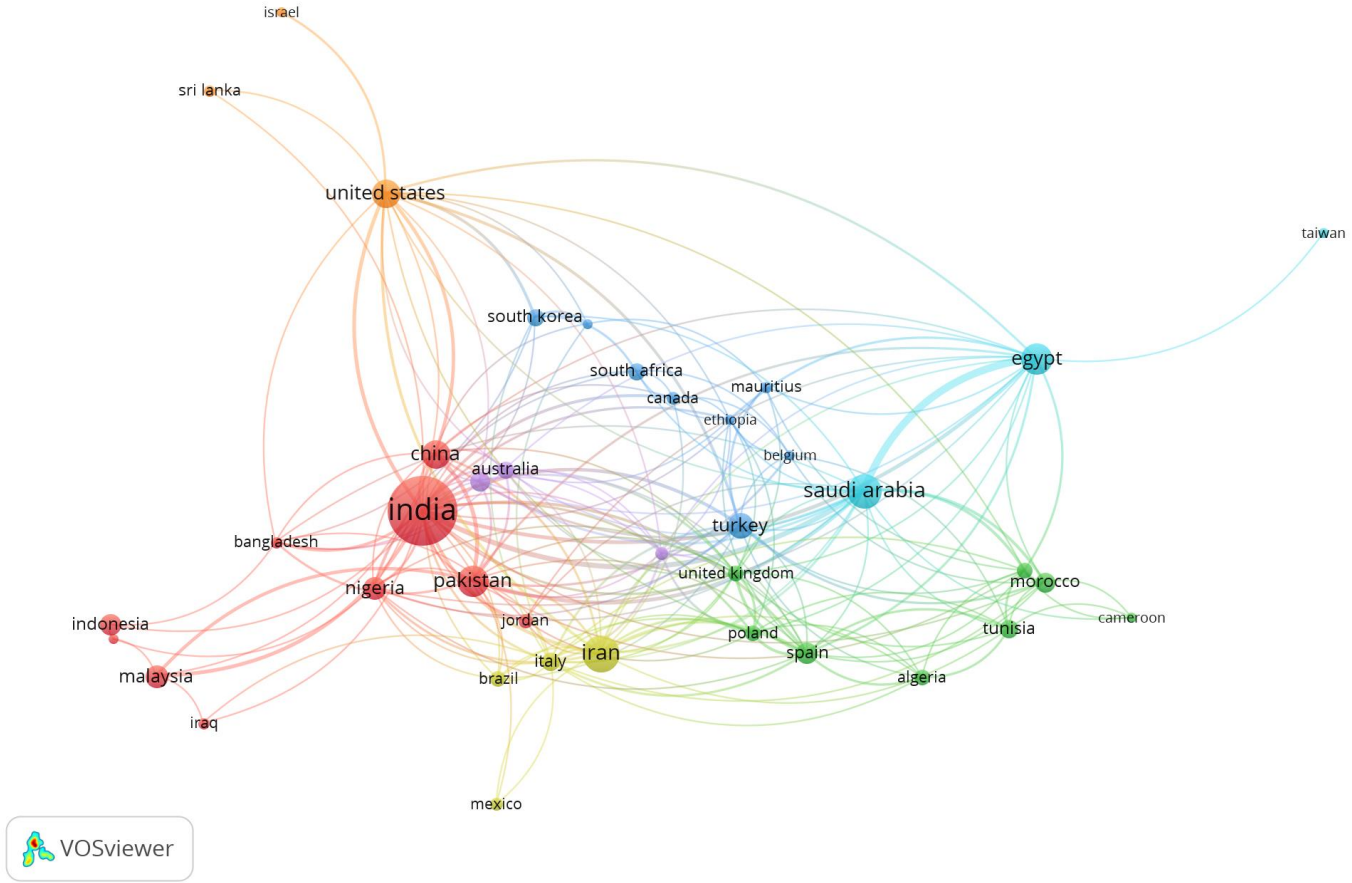


Clinical trials

Translational of prophetic medicine as antidiabetic (co-occurrence network visualization using VOSviewer)



Translational of prophetic medicine as antidiabetic by country



Translational of prophetic medicine as anticancer (co-occurrence network visualization using VOSviewer)

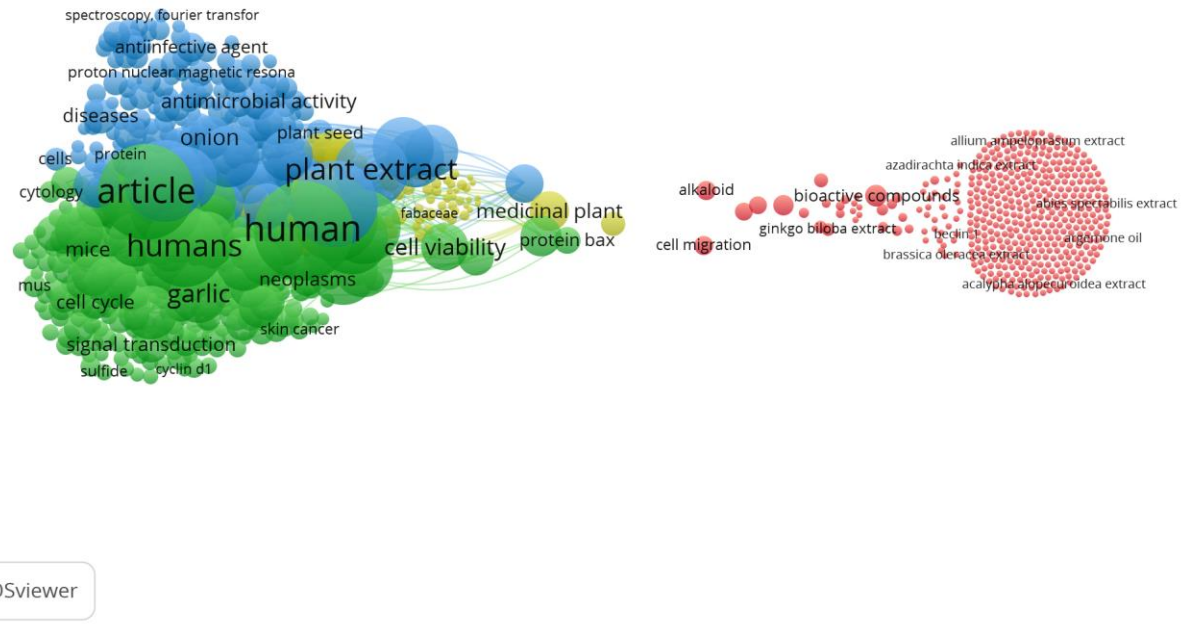
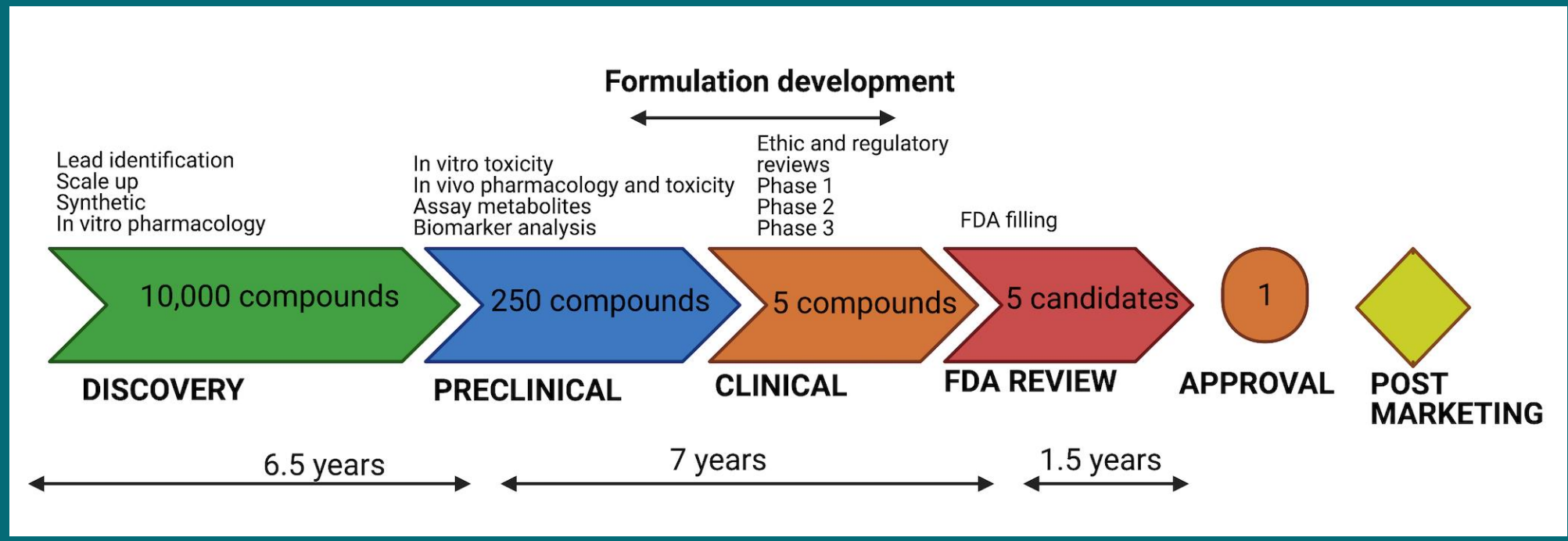


Chart: Drug/herbal discovery and development



COST: USD 1 billion
Duration: 12-15 years

Herbs used in traditional Medicines Jamu in Nusantara

What are the challenges?

1. **Dosage**
2. **Stability**
3. **Standardisation**
4. **Hygiene**
5. **Additive/adulteration**

vulnerable to adulteration are diabetes, calm and sleep, sexual dysfunction, pain relief, and rheumatism

Infusion of rhizomes

Commercialised traditional medicines

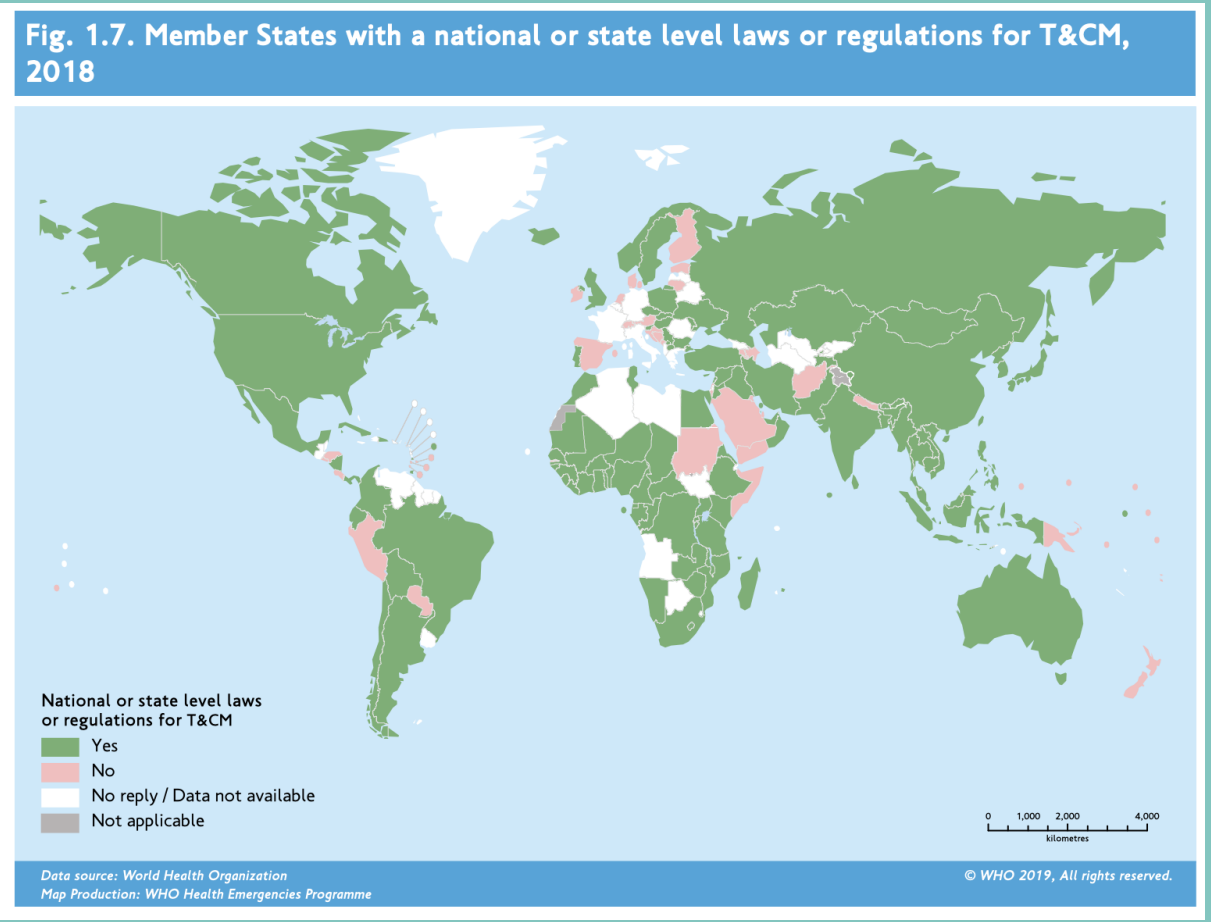
- In the form of extract (Jamu)
- Standardized active the compound (preclinical/obat terstandar)
- Measured dose (Clinical/Biofarmaka)
  - GMP process
  - Increased stability

Herbal medicine preparation

- Extracts
- Decoction
- Tincture
- Syrup
- Eyewash

Traditional medicine (TM)-Global market demand

- Demand
  - In Africa (90%) and in India (70%) of the population depend on traditional medicine
- (TCM)~ 3000 years
- Top selling botanical: *Ginkgo biloba, Allium sativum* (garlic), and *Panax ginseng*
- 177 drugs approved worldwide for treatment of cancer, more than 70% are based on natural products or mimetics
- Regulations



(Wachtel-Galor & Benzie, 2011)

In Indonesia

- 30,000 plants potential
- 1,845 species used as medicine
- Use by 70% people in rural area
- Diseases:
  - Cancer
  - Arthritis/rheumatism
  - High cholesterol
  - Stroke
  - Diabetes
  - Kidney disease

https://ipb.ac.id/news/index/2020/7/as-many-as-80-percent-of-the-world-medicinal-plants-in-indonesia/3fd04650da10a2f332506fa46c92288f

Small molecules from NATURE used as drugs

Of the 1,135 new drugs approved from 1981 to 2010, 50 % were of NP origin (natural, derivatives and analogues) (Cragg, 2007)

Facts

95 % of the world's biodiversity has not been evaluated

Opportunity

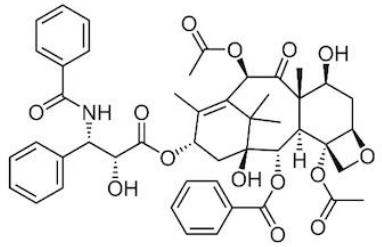
2 million species of plants, animals, fungi and microorganisms (David et al., 2014)

Herbal phytopharmaceuticals which have reached US $60 billion, with annual growth rates of 5–15 % represent a significant share of the total world pharmaceutical market (Naoghare and Song 2010)

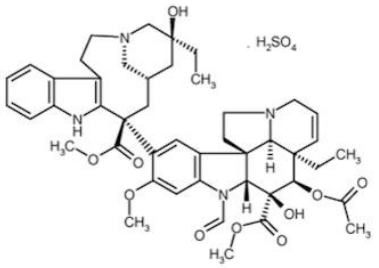
→ Pharma industry
Sponsoring/developing

Taxus brefivolia

Catharanthus roseus



Paclitaxel



Vincristine

Global challenges in drug/herbal discovery and development

New drugs

- Anticancer (targeted)
  - Chemicals
  - Macromolecules
- Antibiotics (multidrug resistant bacteria)

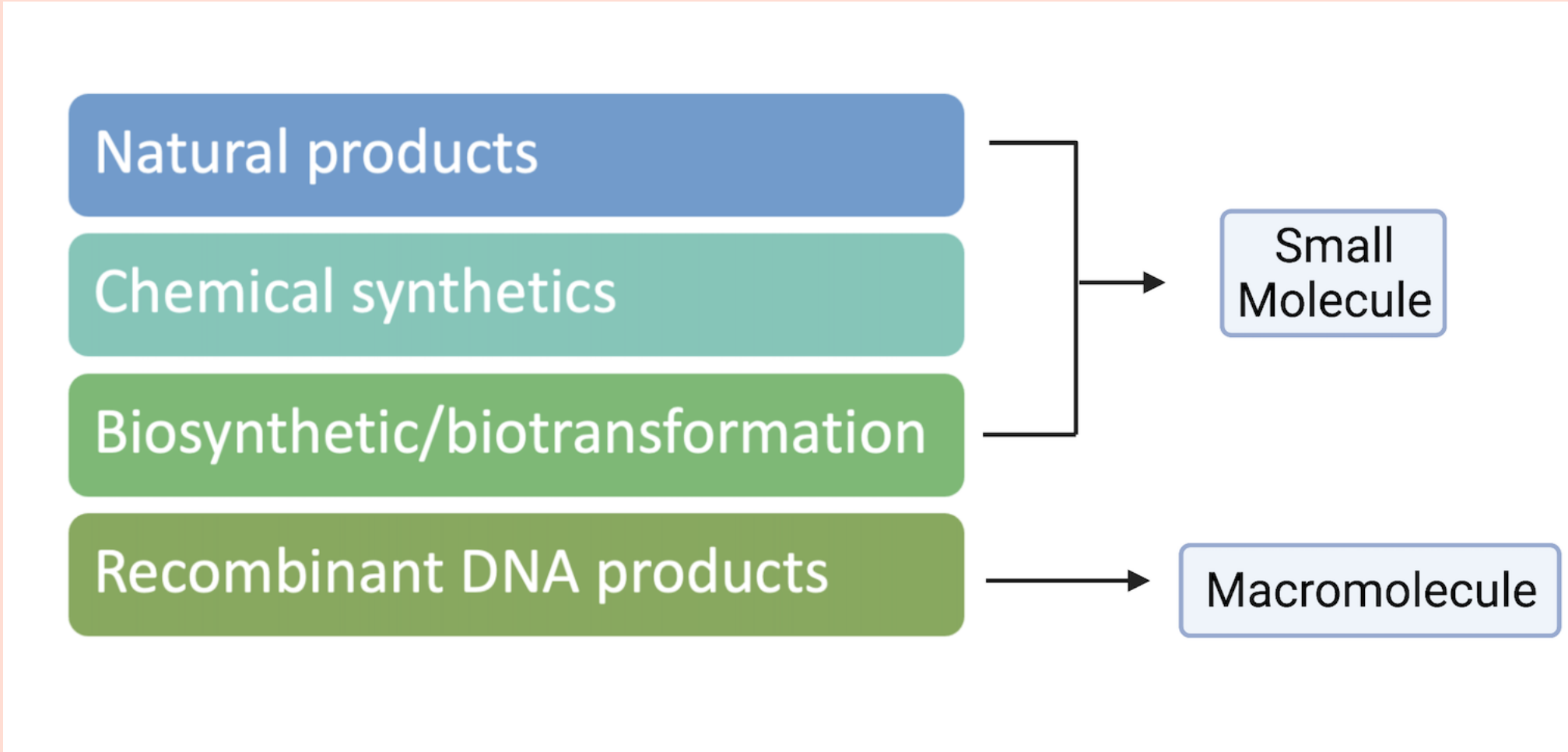
New vaccines

- New strain of virus
  - Covid-19

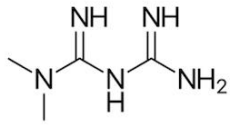
Improved Drug Delivery

- Increase efficacy and reduce toxicity

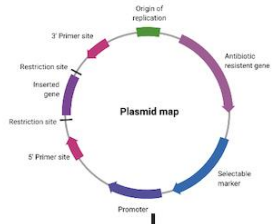
SOURCE OF DRUGS

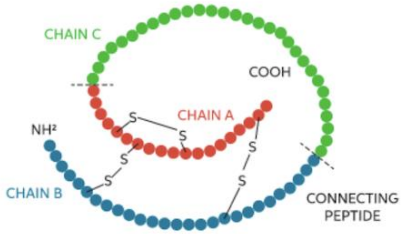


Small molecule vs macromolecule



Metformin



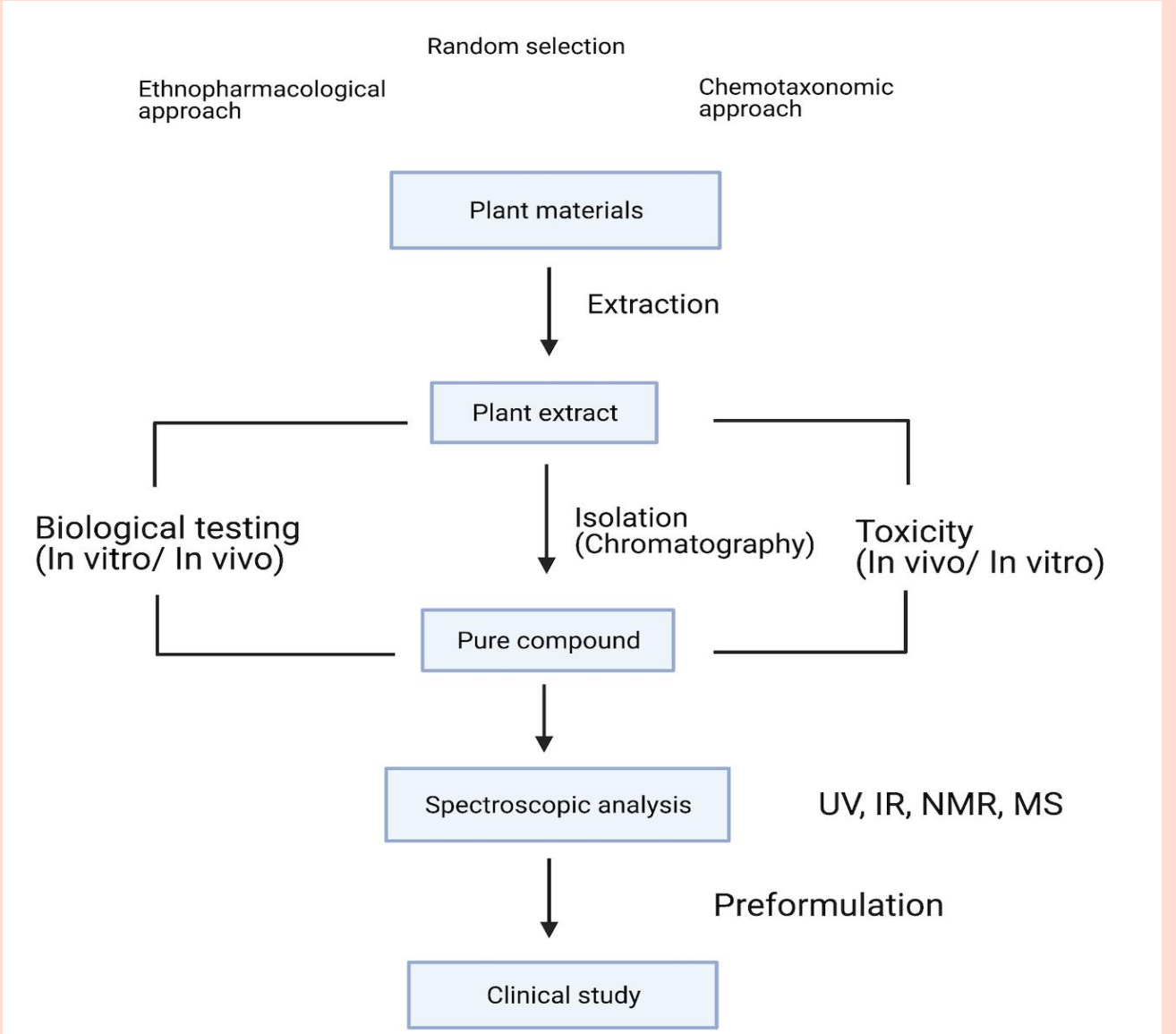


Insulin

Small molecule	Macromolecule
Simple	Large
Single defined structure	Complex structure
Predictable chemical reaction	Derived from living cells
Produce identical product	Identical clone unlikely
Stable	Sensitive to heat
Easy to characterise	Difficult to characterise
Minimal data packet	Robust data packet

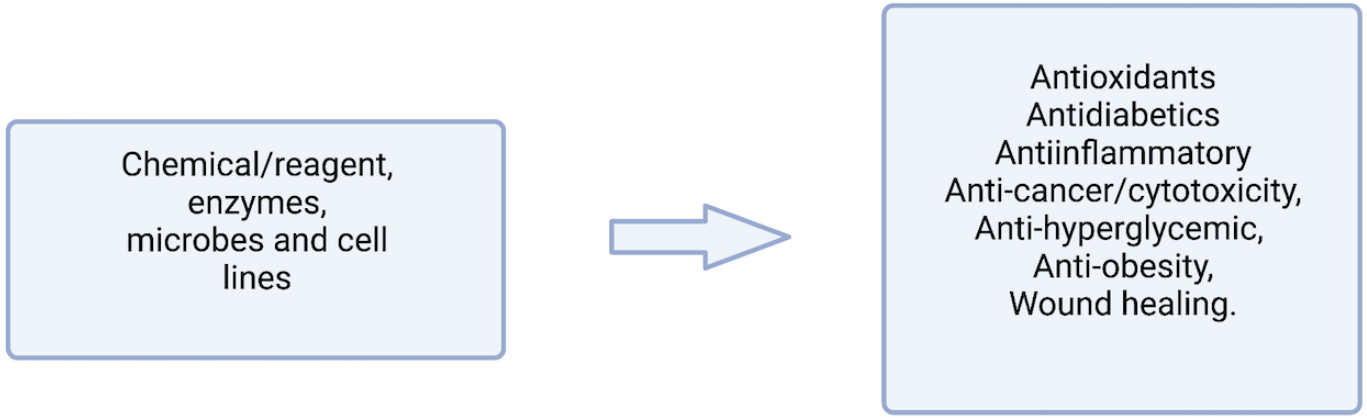
Cauchon et al., 2019

General procedure to develop a new drug from plant sources



In Vitro Studies

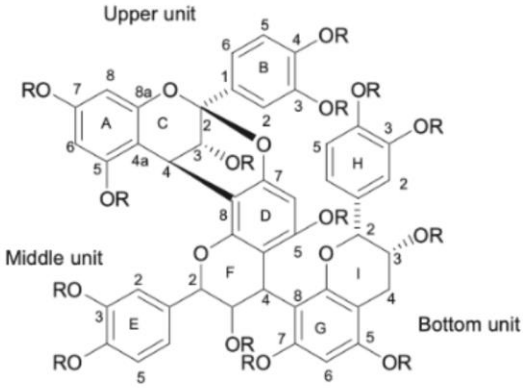
The initial step of drug discovery, all potential lead compounds undergo in vitro pharmacology testing



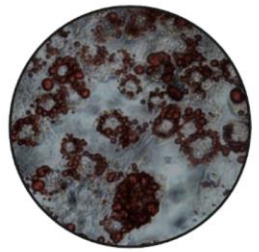
Cinnamon- Antihyperglycaemic-adipocyte cells

Cinnamon bark

Cinnamtannin B1

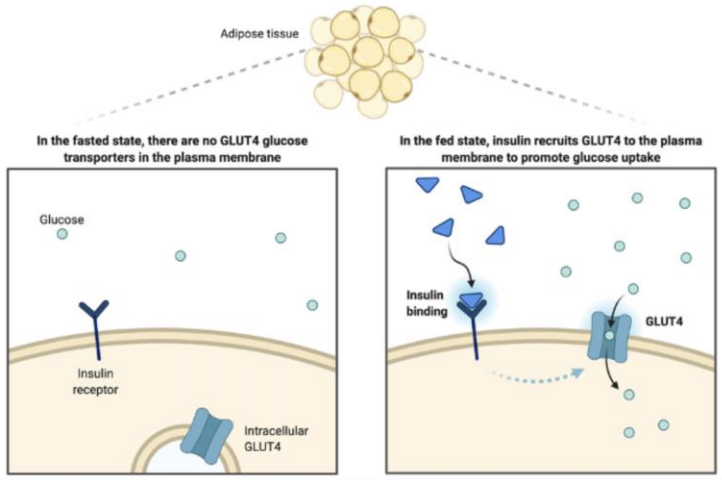


Adipocyte cells-stained



Insulin mimicking activity

Adipocyte cells



TheStar Sweet hopes for diabetics

TOPICS ▸ Flame on Olympics | Sabah & Sarawak | The New Normal | In 500 Words | Covid-19 Watch | EEA 2021 | True or

Sweet hopes for diabetics

NATION

Friday, 06 Jan 2006
12:00 AM MYT

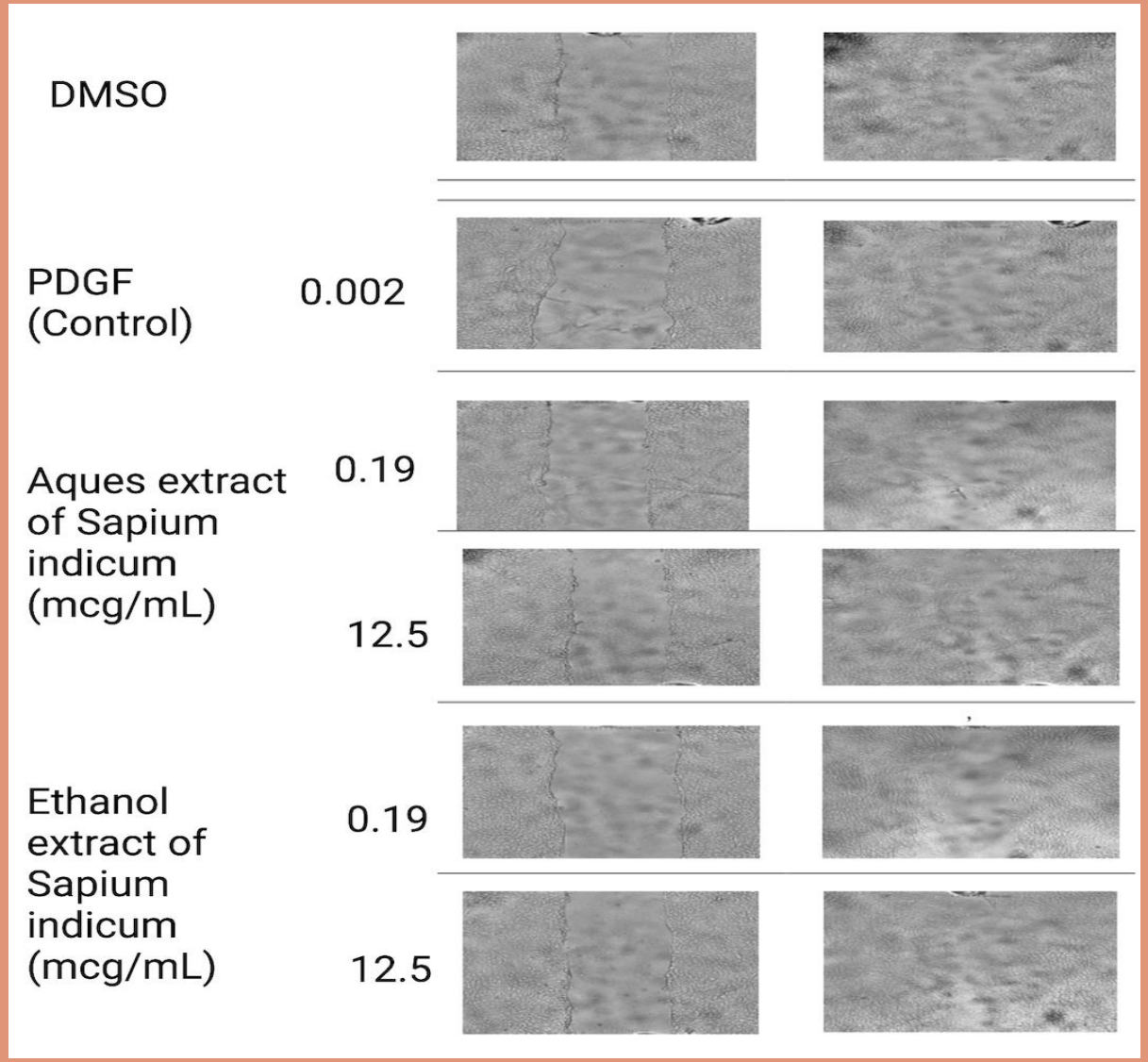
By HAMDAN RAJA ABDULLAHnewsdesk@thestar.com.my

MUAR: Good news for diabetics. A three-year study carried out by Universiti Teknologi Malaysia in Skudai has confirmed previous findings that cinnamon has the potential to lower sugar levels.

UTM research and development manager Prof Dr Mohammad Roji Sarmidi said yesterday their research showed that the spice, known as *kayu manis* locally, has positive

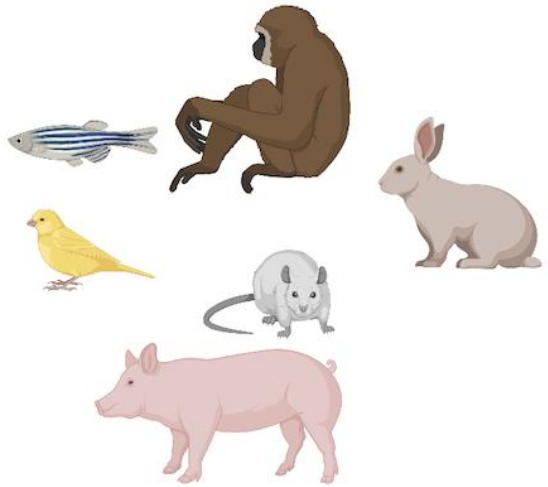
Related News

Wound healing-using cell culture



Animal study

Animals



Guidelines

OECD
NIH
ICH
CPSEA

3R rules

Reduction,
Refinement,
Replacement

Effects

Pharmacokinetics
Pharmacodynamic
Physiology
Pharmacology

Tests

Antihyperglycaemic
Wound healing
Antitumour
Antinociceptive

Goal

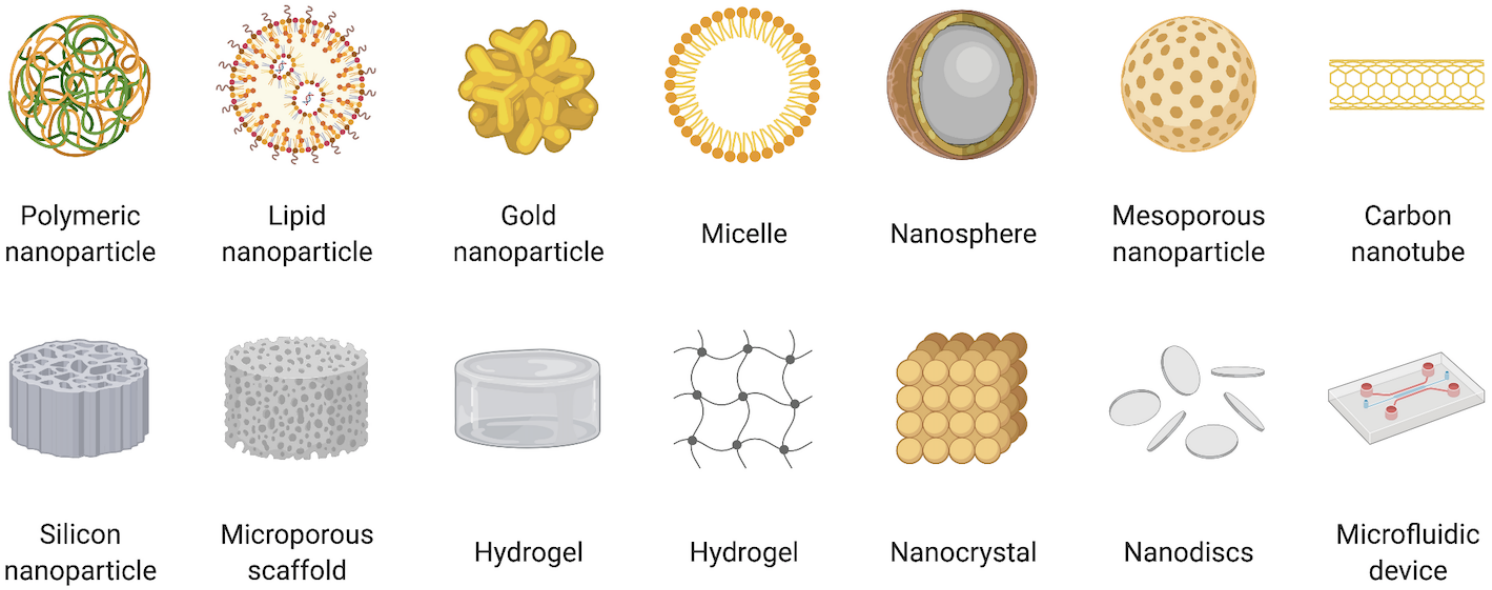
Mechanism of action

DEVELOPMENT

DRUG FORMULATION

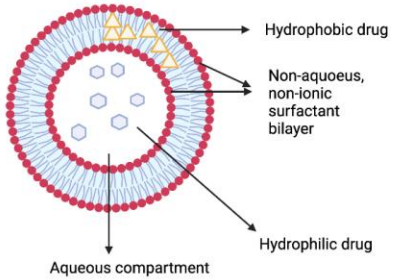
Formulation	Pharmacokinetic, Efficacy, Toxicological studies	Biopharmaceutical Classification System	Nanotechnology
Development step	Function	Challenges	Strategy

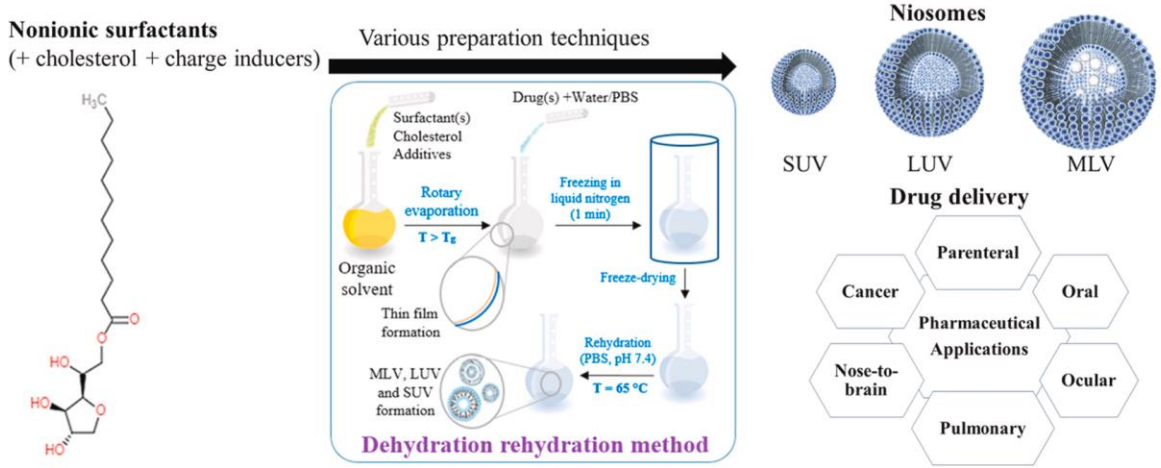
NANOFORMULATION



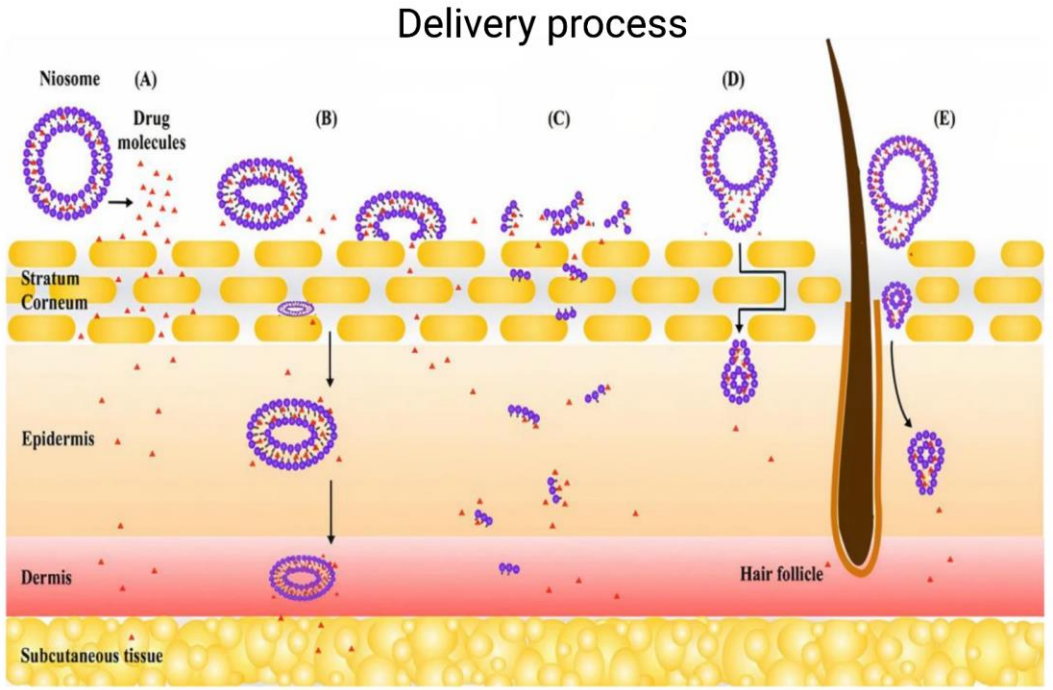
Biocompatible, biodegradable, non-immunogenic, have a long shelf life, exhibit high stability.

NIOSOMAL FORMULATION





Masjedi et 2021, https://doi.org/10.1016/j.jddst.2020.102234



Bhavni et al, 2020.https://doi.org/10.1186/s43094-020-00117-y

Aceclofenac Proniosom, Rana et al 2020
Raloxifene tansfersome, Mahmood et al 2017

Herbal Legislation

- The range between therapeutic and toxic doses is called “therapeutic window.”
- The word “natural” is good, every year, huge damage is caused by the inappropriate use of the so-called natural products.
- Approximately 123 million people use these products for various purposes,
  - obesity,
  - to prevent cancer,
  - to ease pain,
  - to enhance sexual performance,
  - to stimulate mood,
  - concentration, and memory,
  - to enhance immune responses,
  - to increase muscle mass and
  - physical performance

FDA has registered about 2900 cases of toxic effects, including 104 deaths caused primarily by the abuse of *Ephedra*.

Three fundamental principles in herbal development and/or clinical use (Lietman, 2013)

1. Standardization and regulation (rigorously enforced) of the product being studied or being used clinically.

2. Scientific proof of a beneficial clinical effect.

3. Scientific proof of safety (acceptable toxicity) for the patient

Quality Assurance and Quality Control

- Identity (Pharmacognostical testing, Qualitative and Quantitative with reference)
- Purity-Instrumental testing (HPLC, GC)
- Contents-Instrumental (HPLC, GC)
- Microorganism testing- Microbial growth test
- Stability testing-ICH guidelines

Variable composition

- Herbs do not have consistent and standard composition
- Numerous chemical constituent in different part (e.g roots, leaves and fruit)
- Factor affecting the variability: climate, growing conditions, time of harvesting, post harvesting and storage.

Contamination

- Misidentification of species
- Adulterations
- Heavy metal and pesticides

Marker compounds

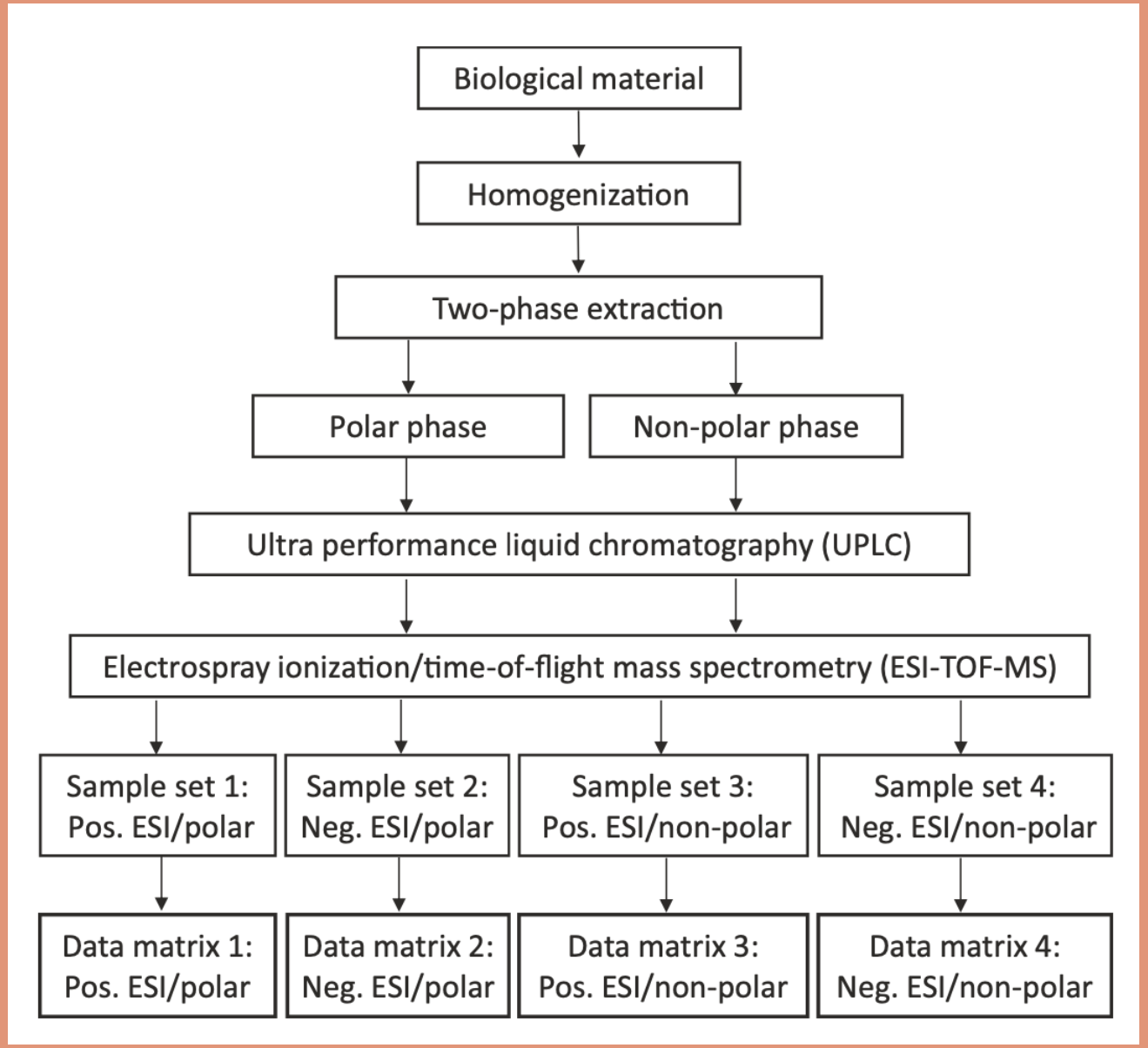
- Ideal chemical markers should contribute to the therapeutic activity.

- Main application of chemical markers
  1. Identification adulterations
  2. Differentiation of multiple source
  3. Determining best harvest time
  4. Confirmation of collection site
  5. Quality evaluation of herbal parts
  6. Stability testing

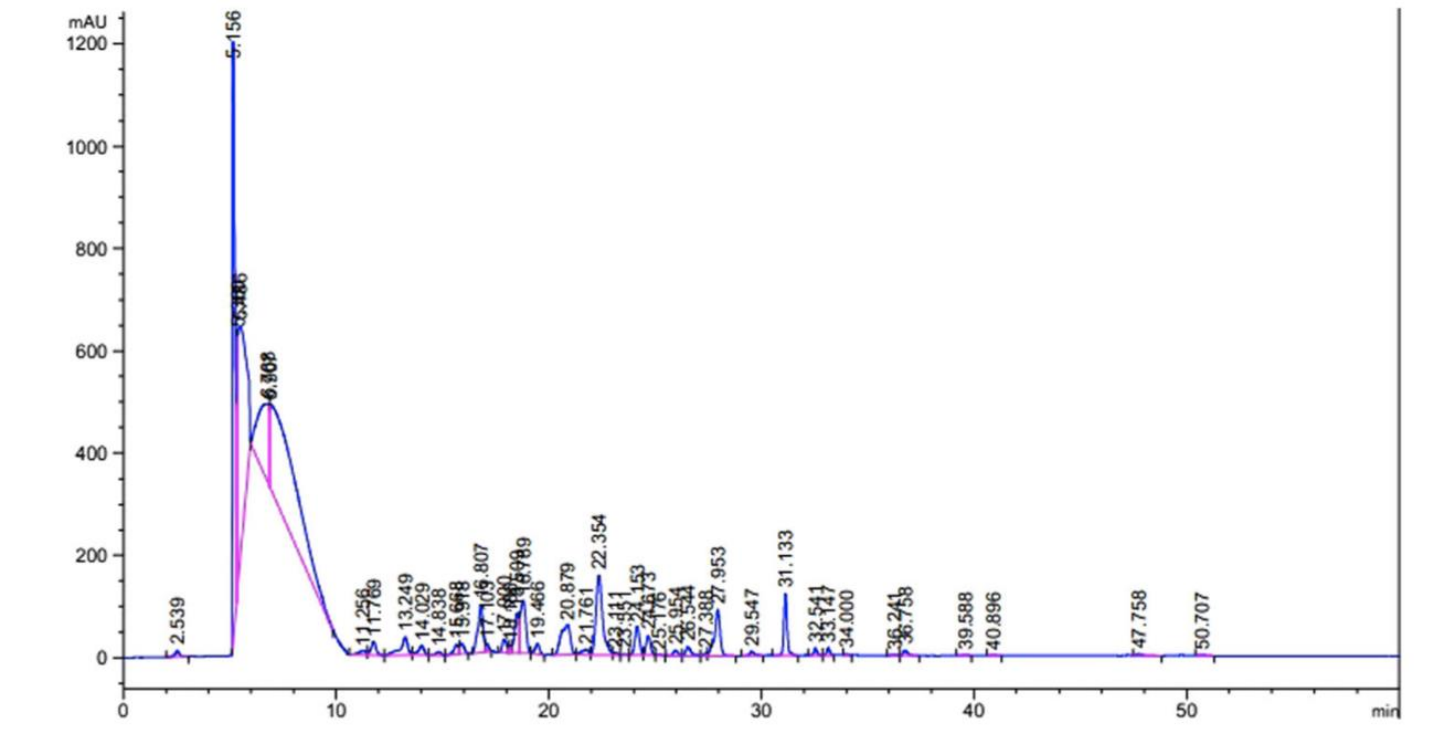
Analytical in Quality Control

- High Performance Liquid Chromatography
- Gas Chromatography
- Thin Layer Chromatography
- Capillary Electrophoresis
- LC-MS fingerprint

- Metabolite fingerprinting is a comprehensive and comparative nontargeted metabolomics approach



Metabolite fingerprinting
HPLC-DAD identification of phenolic compounds in Olax nana leaves



Peak	RT (min)	Peak height (mAU)	Peak area %	Proposed identity of compound*	HPLC–DAD λmax (nm)
1	2.5	13.29053	0.320	Ascorbic Acid	244
2	5.2	1168.32886	14.41	Gallic acid derivative	273, 279, 288
3	5.3	504.33762	3.19	Gallic acid derivative	280
4	5.8	456.65558	17.81	Hydroxybenzoic acid derivative	280
5	6.3	151.39925	8.20	Hydroxybenzoic acid derivative	274
6	6.9	163.31013	25.57	Gallic acid derivative	271, 278, 287
7	11.1	8.41879	0.33	Kaempferol-7-O-glucoside	254
8	11.6	26.59516	0.70	*p*-Coumaric acid derivative	313
9	13.2	35.75774	1.36	Isovitexin-4-O-glucoside	254
10	14.3	18.4162	0.57	Caftaric acid	242; sh 298; 328
11	14.9	6.63179	0.17	Gallic acid derivative	280
12	15.5	19.11495	0.46	Hydroxybenzoic acid derivative	278
13	15.7	19.45154	0.43	Hydroxybenzoic acid derivative	278
14	16.9	92.68282	2.47	p-Hydroxybenzoic acid	256
15	17.0	15.39486	0.23	Caffeoylmalic acid	327, 300, 268
16	17.5	26.84283	0.60	bis-HHDP-glucose	232
17	18.1	14.13607	0.21	Quercetin-3-O-triglucoside	268; 340
18	18.3	77.88322	1.70	Galloyl-HHDP-glucose	232
19	18.9	102.11224	2.93	Apigenin-7-O-rutinoside	254
20	19.9	19.88177	0.46	P-coumaric acid derivative	228, 316

HPLC-DAD chromatogram of methanolic extract of Olax nana
(Ovais et al., 2018)

Conclusion

- WHO promotes the use of traditional medicines (particularly herbal medicines) in primary health care
- Some countries rely on herbal medicine in their primary health care.
- Herbal medicine development requires scientific support to ensure the quality, efficacy and safety of the product

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Thank You

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