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Chemical Derivatization of Phytochemicals: A Constant Source of New Drug Molecules

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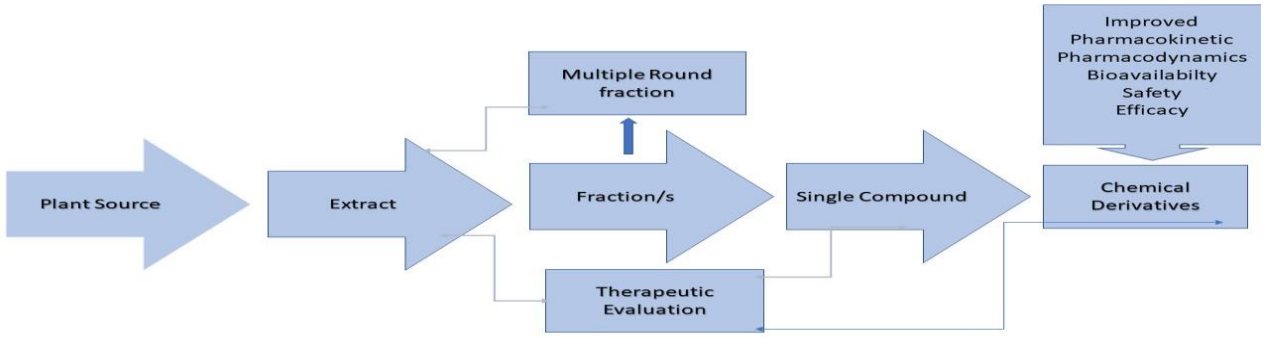
Abstract: An overview of the well-known function of phytochemicals as a source of fresh drug leads is provided. Combinatorial chemistry has raised hopes for the discovery of novel chemical entities with considerable molecular activity and desirable pharmacological characteristics. In addition to being used as precursor materials for analogue design and synthesis as semisynthetic new drug entities exhibiting higher therapeutic efficacy, phytochemicals and their analogues exhibit high chemical diversity, apex biochemical specificity, and therapeutic efficacy. Identification of the ideal candidate phytomedicine by bioassay-guided fractionation and separation of desired phytoconstituents is required for the start or design of new phytochemical entities. In many instances, structural alteration of phytomedicines is necessary to improve the physic-chemical and pharmacokinetic activities of plant-derived compounds, which results in altered therapeutic action and increased selectivity. Exploring the novel derivatized chemical entities is encouraged by semisynthetic derivatives' overall favourable preeminence. The goal of the current review is to provide an overview of phytochemical chemical derivatization.

Keywords: Phytochemicals, Semisynthetic derivatives, Synthetic drugs.



Graphical Abstract: Phytochemicals in the drug development

Introduction: Plants have long been used by people to meet basic needs like food, clothing, shelter, and cures for a wide range of illnesses. Since the beginning of time, man has relied on nature to meet his fundamental requirements and has also investigated its riches and employed them to treat illnesses. Ancient civilizations used traditional medicine, with knowledge transferring from one generation to the next. Traditional medical practises based on plants continue to be crucial to healthcare, and usage across cultures has been well-documented [1-2]. Plant-derived traditional medicines were the primary source of healthcare for almost 65% of the world's population, hence they play a significant role in the healthcare system [3]. Through the use of plant material as an indigenous treatment in folklore or traditional systems of medicine, plant-derived medications first appeared in contemporary medicine. Having higher chemical diversity and being preferred to synthetic combinatorial compounds, photochemicals are typically regarded as safer than synthetic pharmaceuticals. Additionally, the metabolites from plants have more stereogenic centres, heteroatoms in a variety of ratios, favoured core ring scaffolds, and therapeutic efficacy [4-5]. Isolated compounds from well-known plant sources were used as excellent starting points for the design and synthesis of analogues. Although the valuable lead compounds are made of natural materials, it is uncommon for these materials to be used directly in clinical settings [6]. Because natural products and their semi-synthetic derivatives are valuable sources of new drug candidates with a variety of biological and pharmacological activities, structural modifications of isolated compounds are therefore necessary in many situations [7-8]. It's fascinating to see that the majority (21%) of the total medical contribution is made up of semi-synthetic derivatives. Excellent examples of changes that improved biological activity are increasing lipophilicity and adding halogen atoms to natural compounds [9].

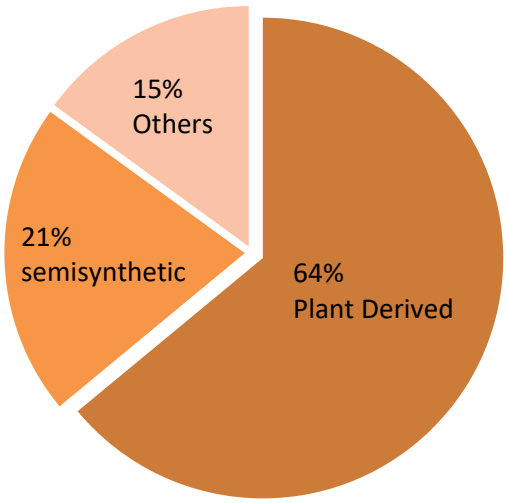


Fig 1: Utilization of Plant derived medicines, Semisynthetic medicines and other systems of medicine

The structural change is used in accordance with standard medicinal chemistry principles to improve therapeutic efficacy, selectivity, pharmacokinetics, and physicochemical properties. The current drug discovery paradigm used by large pharmaceutical corporations and technical constraints on finding novel compounds with desirable activity present hurdles for the development of new semi-synthetic drugs. Structures must be changed when creating an analogue in order to increase efficacy, decrease toxicity, or improve absorption. This is frequently done by adding or removing particular functional groups.The current review summarises the design, chemical alteration, and natural sources of the parent natural substances. This article also aims to present a summary of the biological functions of their equivalents.

Chemical derivatization of natural products:

Alkaloids

Alkaloids are secondary metabolites that include nitrogen and are very common in nature all over the world. They have a variety of biological actions. The first alkaloid, morphine, was extracted from opium in 1805 and it is still a significant therapeutic compound [10]. There are currently more than 20000 alkaloids known, and many of these have been used in medicinal settings. At least 60 plant-derived alkaloids have currently received drug approval in a number of

nations [11]. Daily-consumed purine alkaloids are few in number and are primarily present in tea, cocoa, and coffee. Most alkaloids are pharmacologically active or dangerous when taken in large quantities; they demonstrate a wide range of biological properties, including anticancer, antibacterial, anticholinergic, antihypertensive, antidepressant, anti-inflammatory, and antiulcer [12].

Table 1: Few alkaloids used in marketed medicines

Alkaloid name	Applications	Example product
Ajmaline	Antiarrhythmic agent	Aritmina™, Gilurytmal™, Rauwopur™, Ritmos™
Caffeine	Neonatal apnea, atopic dermatitis	Agevis™, Anlagen™, Thomapyrine™, Vomex A™
Codeine (Methylmorphine)	Antitussive, analgesic	Antituss™, Codicaps™, Tussipax™
Lobeline	Anti-smoking, asthma, cough	Citotal™, Lobatox™, Refrane™, Stopsmoke™
Morphine	Pain relief, diarrhea	Diastat™, Duromorph™, Oramprph™, Spasmofen™
Quinine	myotonic disorders	Adaquin™, Biquinate™, Quinoctal™, Zynedo-B™
Taxol (Paclitaxel)	ovary carcinoma	Taxol™
Vinblastine	Hodgkin's disease, testicular cancer, blood disorders	Periblastine™, Velban™, Velbe™, Velsar™
Vincristine	Burkitt's lymphoma	Norcristine™, Oncovin™, Vincrisul™

Ajmalin: Ajmalin and ajmalicine are the medicinally important terpenoid indole alkaloids. The most important indole alkaloid is clinically useful anticancer agent. Ajmalicine is used in the treatment of circulatory disease. Ajmalicine was found to occur in *Uncaria elliptica* and *Petchiaceylanica* , whereas its 10,11-dimethoxy derivative, reserpiline , and the C-20 epimer of reserpiline, isoreserpiline, have been isolated from *Neiosospermaoppositifolia* .

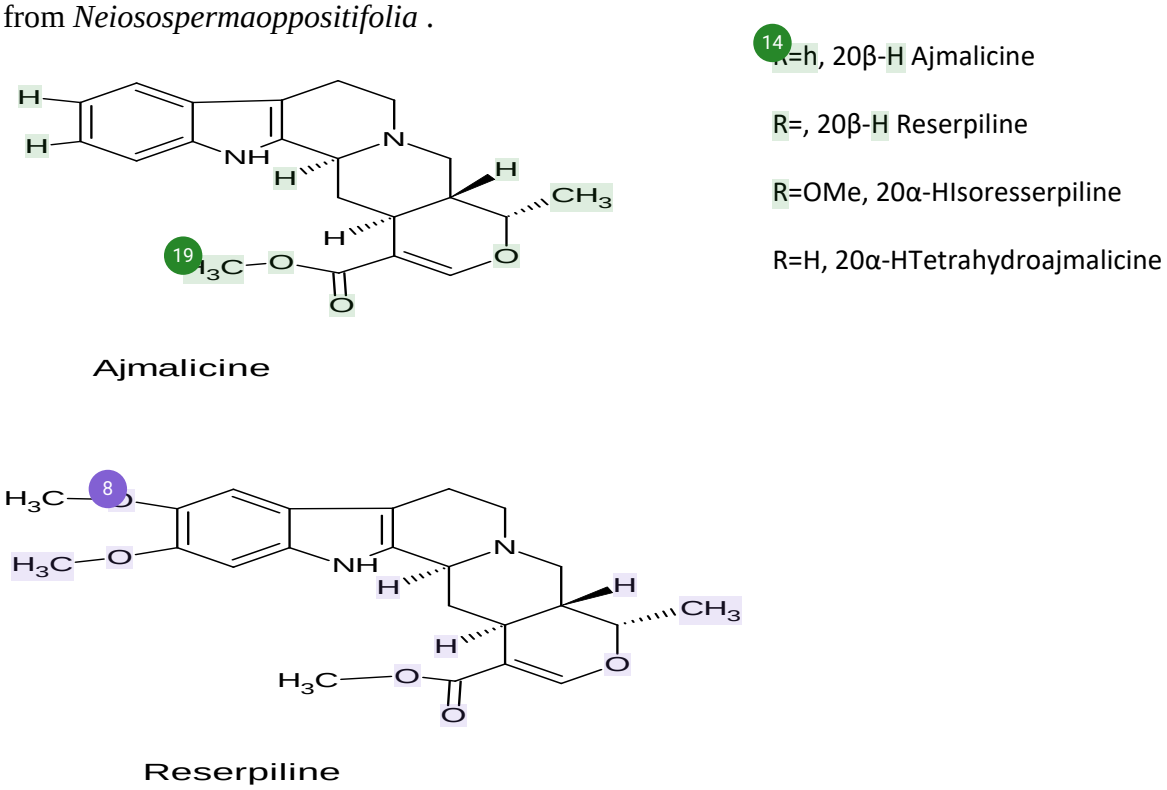


Fig 2: Chemical derivatives of Ajmalin

Caffeine: Understanding the mechanism and molecular effects of oxidative damage to purine bases, which occurs mostly at C-8, requires a special interest in the oxidation of purines. Caffeine and its equivalents involve the embedded purine ring structure being oxidised at C-8. No other oxidation products were seen during the extremely selective reaction, which was thought to be caused by the production and rearrangement of the 8,9- or 7,8-oxaziridines [13].

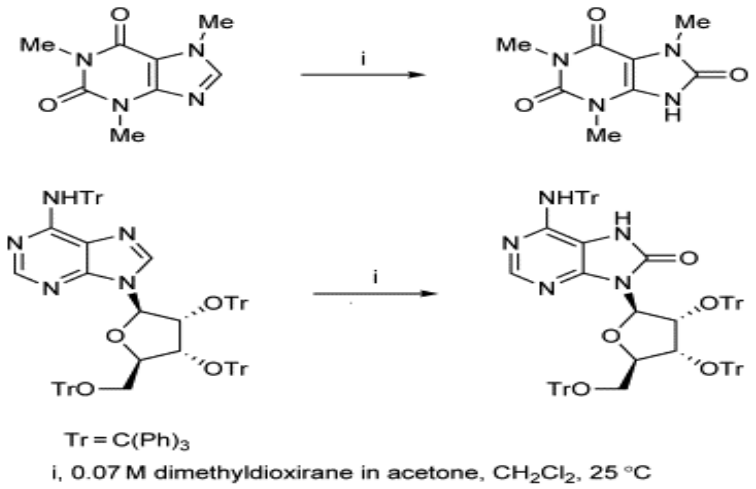
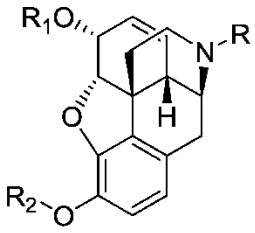
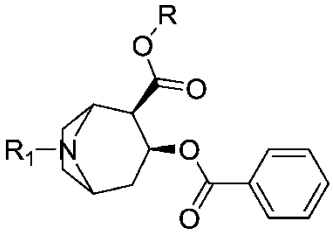


Fig 3: Different chemical derivatives of Purine Bases

Morphine: The opium poppy, or Papaver somniferum, is a plant that naturally contains morphine, a potent narcotic. It is mostly used to treat pain, but it is also frequently consumed recreationally or used to create other illegal opioids. Other opioids like hydromorphone, oxymorphone, and heroin are all made from morphine [14].





Compound	R	R_1	R_2
Norcodein (**1**)	H	H	CH_3
Codeine (**2**)	CH_3	H	CH_3
Morphine (**3**)	CH_3	H	H
Heroin (**4**)	CH_3	Ac	Ac
6-Acetylmorphine (**5**)	CH_3	H	Ac
3-Acetylmorphine (**6**)	CH_3	Ac	H

Compound	R	R_1
Cocaine (**7**)	CH_3	CH_3
Norcocaine (**8**)	CH_3	H
Benzoylecgonine (**9**)	H	CH_3
Cocaethylene (**10**)	CH_2CH_3	CH_3

Fig 4: Various semisynthetic derivatives of Morphine

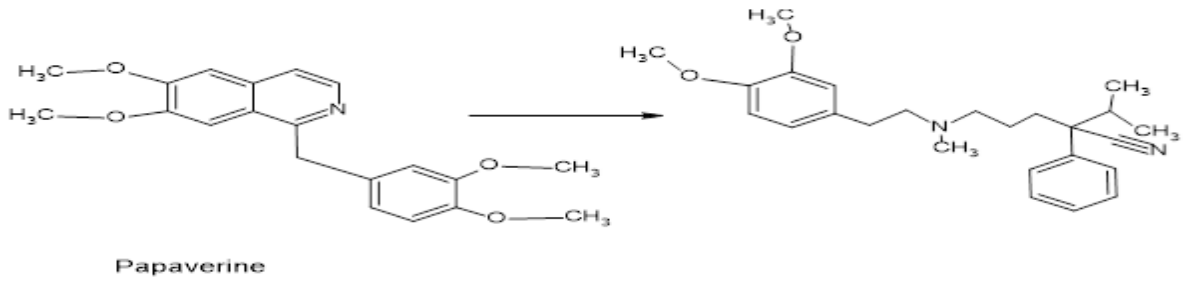


Fig 5: Semisynthetic modification of some alkaloids

Quinine: One of the biggest health problems that the human race still faces is malaria, thus finding more affordable and effective medications is crucial for world health. Indigenous communities in the Amazon region had long employed the bark of cinchona species to treat fevers; this practise was later brought to Europe to treat malaria. Quinine, an antimalarial medicine, was extracted from the bark of various Cinchona species, including C. officinalis. The antimalarial medications chloroquine and mefloquine, which essentially supplanted quinine, were synthesised from quinine. With the emergence of resistance to both of these medications in many tropical places, another plant long used in Traditional Chinese medicine (TCM) to treat fevers, Artemisia annua (Quinhaosu), gained prominence[15]. A promising new natural product lead compound, known as artemisinin, was offered by traditional Chinese medicine. In many nations now, artemisinin analogues are used to treat malaria [16]. In an effort to increase the activity and utility of artemisinin, many analogues have been created. The completely synthetic analogue OZ277 (Fig. 7) [17] and the dimeric analogue are two of the more promising of these.

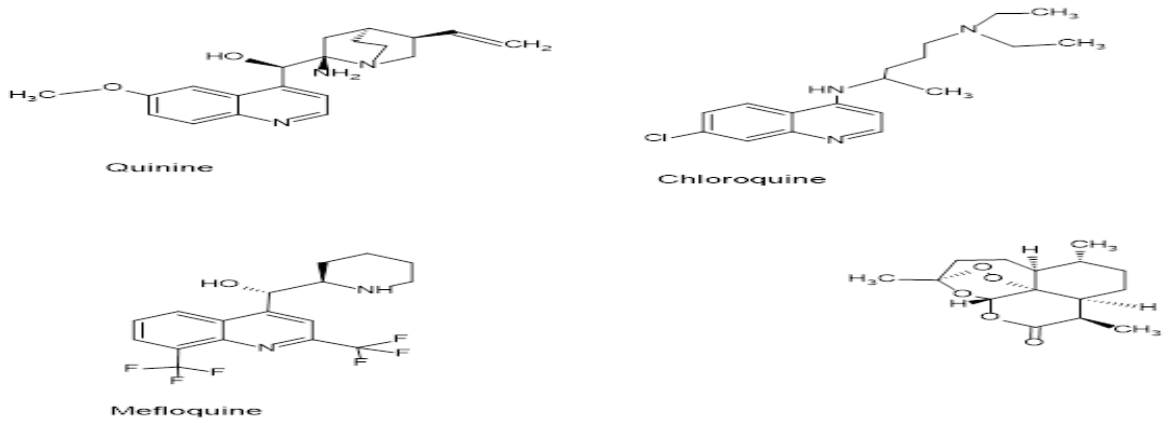


Fig6:semisynthetic analogue of antimalarial Quinine

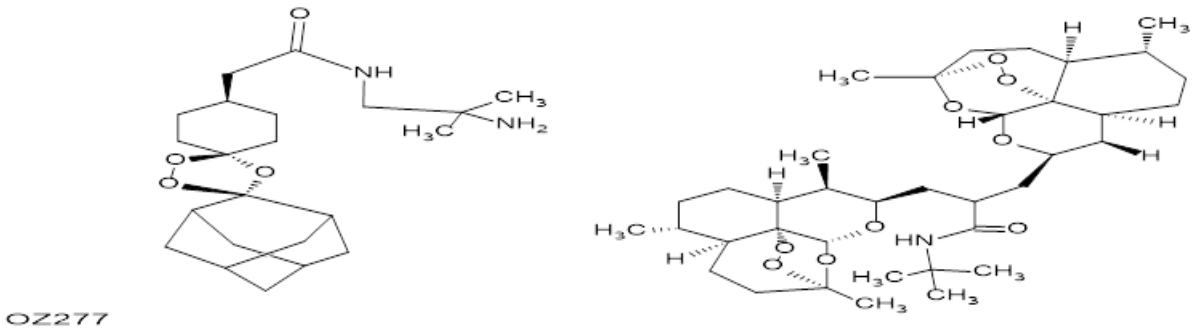


Fig7: semisynthetic analogue of antimalarial Artemisin

Plants have been used to cure cancer for a very long time [18], but many of the claims made for their effectiveness should be considered with some scepticism because cancer is probably not well defined in terms of folklore and traditional medicine [19]. The so-called vinca alkaloids vinblastine and vincristine, as well as the two clinically-active drugs etoposide and teniposide, which are semi-synthetic derivatives of the naturally occurring substance epipodophyllotoxin, are some of the best known [20–22]. They were discovered in the Madagascar periwinkle, Catharanthus roseus.

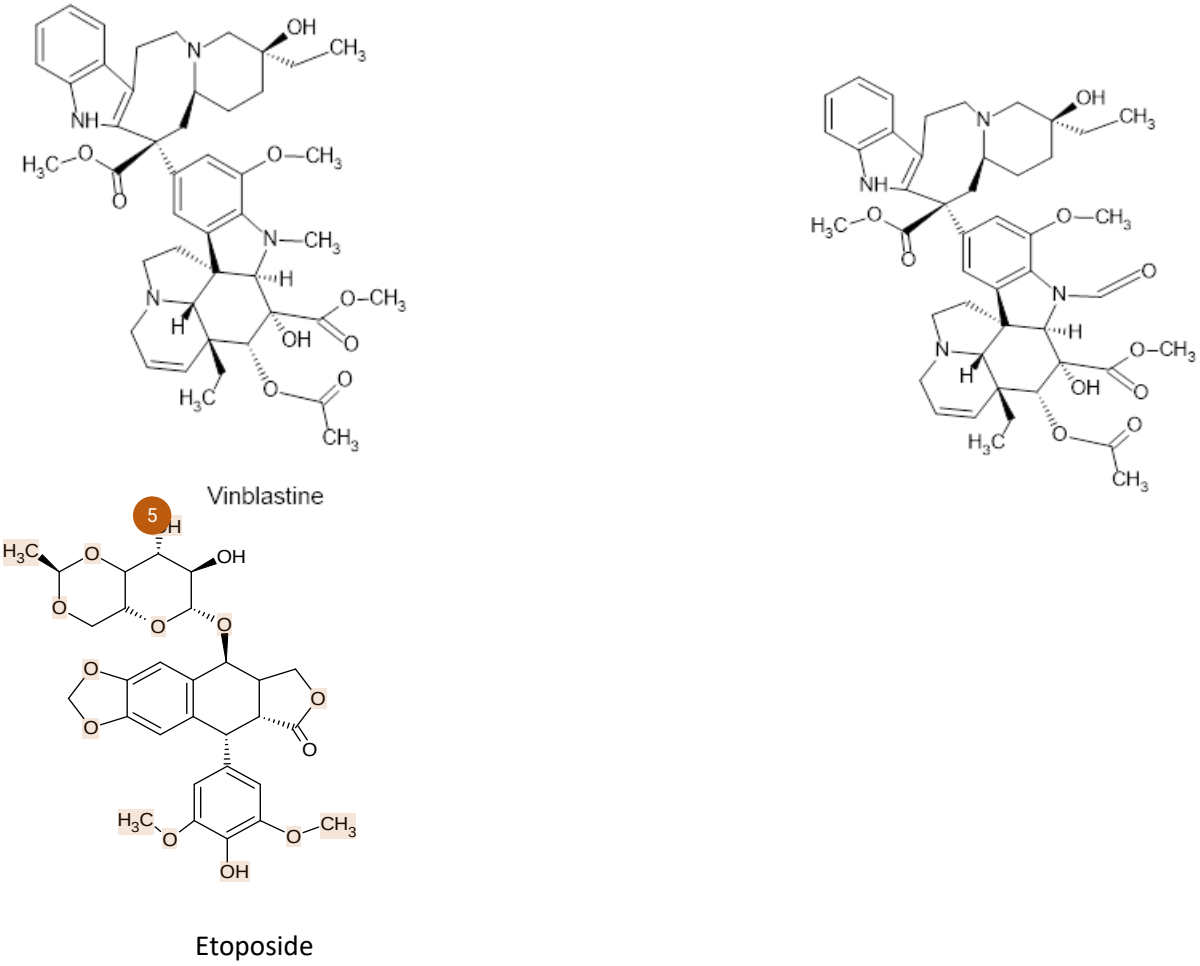


Fig 8: Chemical Modification in anticancer phytochemicals from Vinca & Taxol

Flavone: An essential subclass of flavonoids with a 2-phenyl-1-benzopyran-4-one structure are known as flavones. In complicated diseases like cancer, inflammation, cardiovascular disease, diabetes, and different neurological disorders, the scaffold has been frequently employed for multitargeting. Flavones have a wide spectrum of biological functions, which has sparked interest in the structure-activity connections among medicinal chemists. Low molecular weight polyphenolic phytochemicals called flavonoids are produced by plants' secondary metabolism [23]. The following classes of flavonoids would be distinguished: flavonols (quercetin, kaempferol, myricetin, fisetin), flavones (luteolin, apigenin), flavanones (hesperetin, naringenin), flavonoid glycosides (astragalin, rutin), flavonolignans (silibinin), flavans (catechin, epicatechin), isoflavones (genistein, daidzein), anthocyanidins (cyanidin, delphinidin), aurones (leptosidin, aureusidin), leucoanthocyanidins (teracacidin), neoflavonoids (coutareagenin,

dalbergin), and chalcones (Fig.9). The medicinal potential of numerous natural, semisynthetic, and synthetic flavone derivatives has been investigated. Due of flavones' beneficial effects on oxidative stress-related disorders like cancer and Alzheimer's disease, which are significant metabolic diseases caused by oxidative stress. Flavones can undergo a variety of structural modifications to produce products with the high yield, purity, and desirable quality. These structural modifications include reduction reactions, base-induced degradation, oxidation, rearrangement, substitution, addition, condensation, and reactions with organometallic reagents.

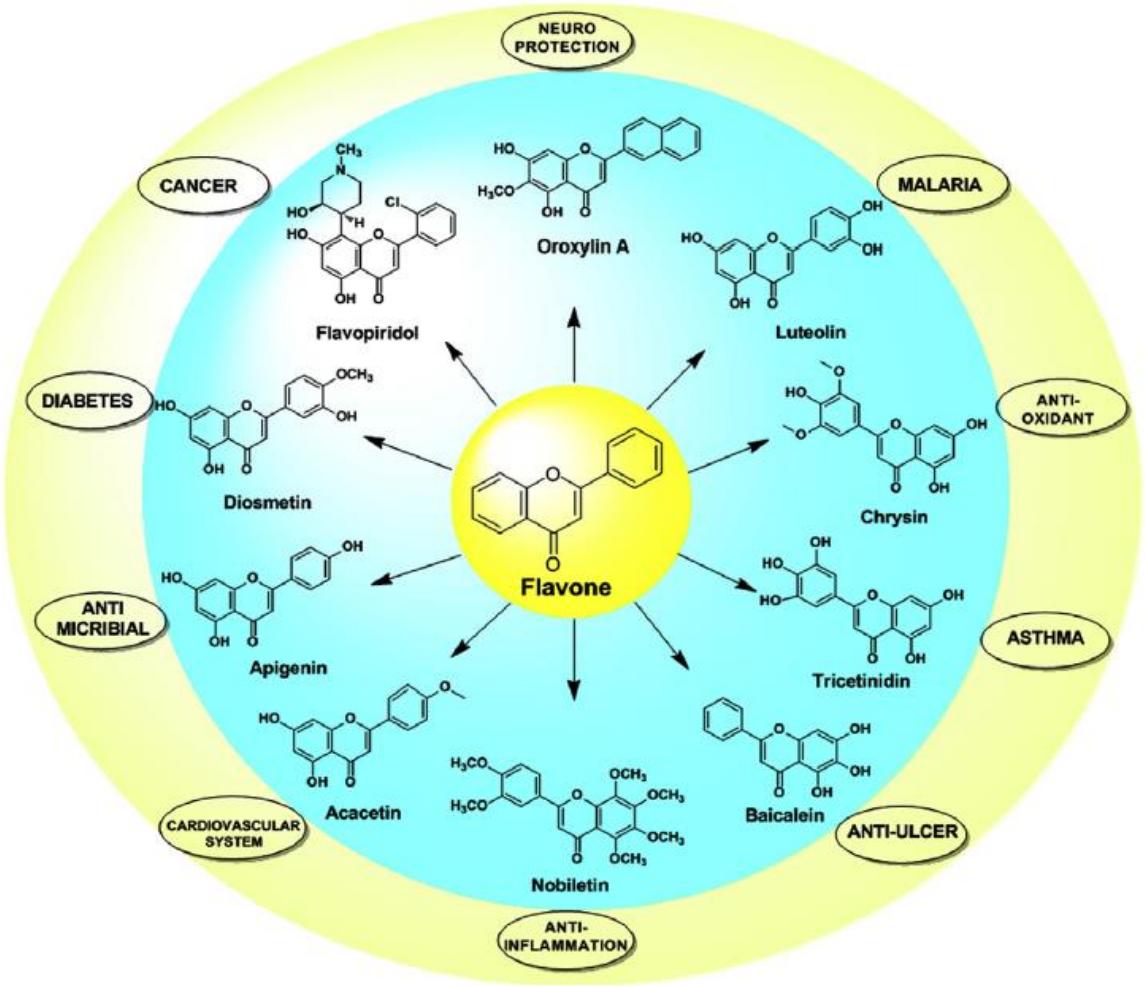


Fig 9: Different Flavones with vast therapeutic activity

Lignans: The broad group of phenylpropane derivatives known as lignans are widely present in higher plants and have a significant role in both food and medicine. Their varied structures (dimers, trimers, or tetramers) and pharmacological effects, such as anti-tumor, antiviral,

antimitotic, antihypertensive, and anti-oxidant qualities, have drawn substantial attention. Lignans were chosen as the beginning material to create semi-synthetic derivatives due to the numerous types of bonding of the C6 and C3 units and oxidation of the intriguing structures [24–25].

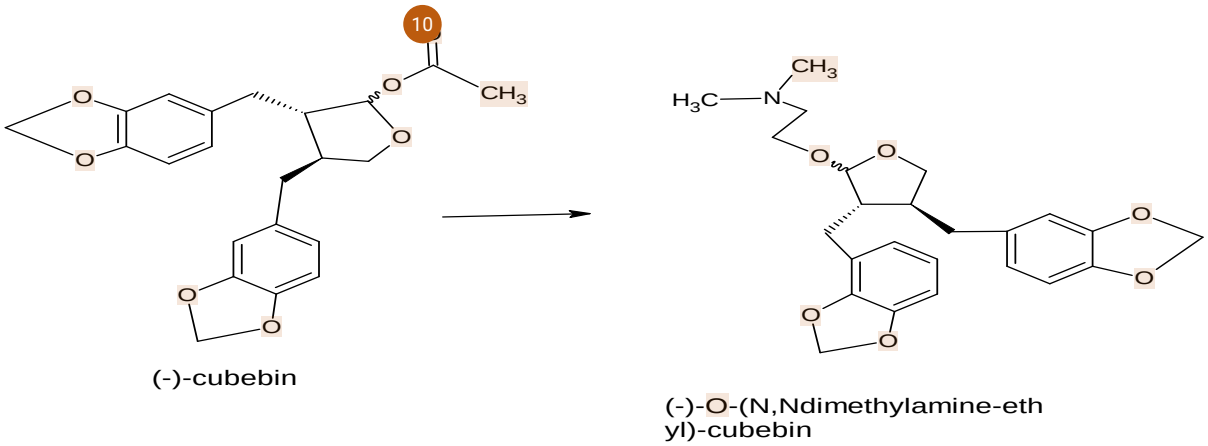


Fig 10: Lignans and Semisynthetic analogue

Phenolic compounds: Polyphenols and phenolic compounds are secondary metabolites that have a variety of uses. owing to their widespread occurrence, variety of chemical makeup, and alluring pharmacological characteristics.Functional foods are a rich source of these phytochemicals. The therapeutic effectiveness of phenolic substances includes antioxidant, antibacterial, cancer prevention, ascorbic acid stabilisation, etc. [26–28].

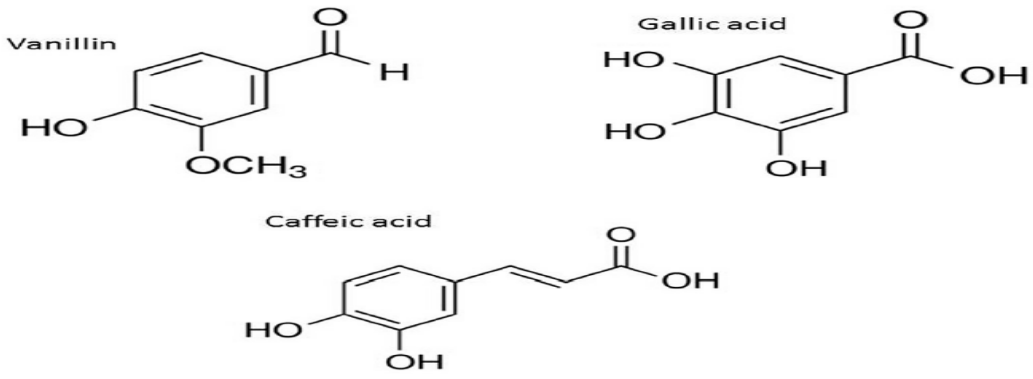


Fig 11: Commonly used Polyphenols for synthesizing analogues

Steroid: The metabolism of cholesterol produces steroids, which have a distinctive cyclo-pentanoperhydrophenanthrene ring motif. Steroids are important for drug development, medical chemistry, and chemical biology. A number of FDA-approved medications with steroid bases are used to treat a range of medical conditions, including inflammation, heart disease, cancer, and allergic response. They also play a significant role in other crucial areas of health-related behaviour, such as fitness and contraception [29–31].

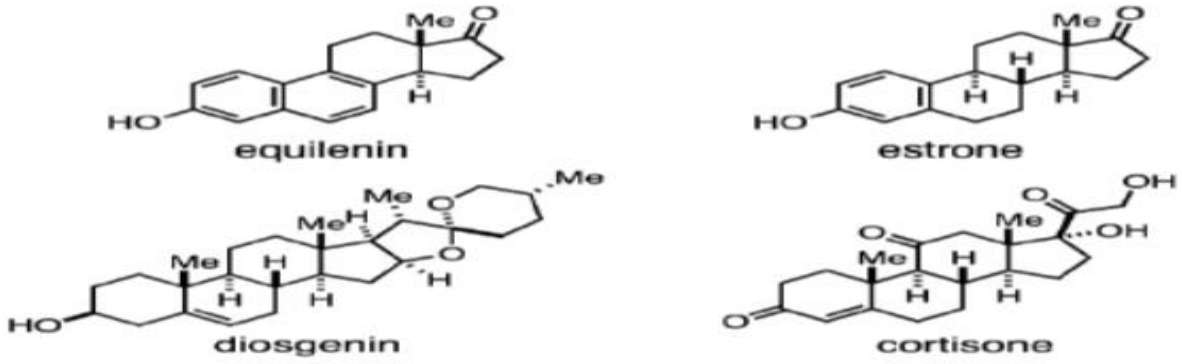


Fig 12: Plant derived steroids and analogue

Conclusion. The use of natural materials and their semi-synthetic derivatives as sources of innovative medication candidates with a variety of therapeutic effects is exceptional. Resources for developing novel therapeutic compounds are already available or are being developed quickly. Numerous altered semisynthetic drug compounds are produced thanks to the development of synthetic biology technologies. The importance of a semisynthesis as a strategy for boosting the biological activity of starting natural products has been well researched. Numerous promising natural and/or semi-synthetic phytochemicals fit the bill to be considered as possibilities for use in drug discovery. The active chemicals are being isolated from the species that displayed high biological activity during screening using bioassay-guided fractionation. various scientific studies might be used to develop medicines for various illnesses. In order to derive the compounds with the appropriate pharmacokinetics, pharmacodynamics, and

therapeutic efficacy, more research is required. These compounds could then be used as leads and scaffolds for the creation of novel medications.

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