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NATURAL PRODUCTS: THE LEADING INDUSTRY AS PHARMACEUTICAL DRUGS

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ABSTRACT

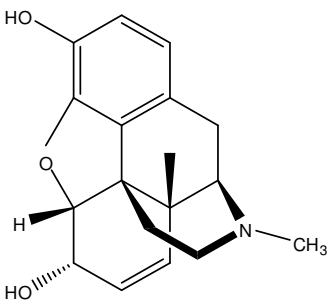
This review is being focused on the importance and emergence of natural products in therapeutic field due to their multiple sources and their multiple biological use. The uses of natural products are as old as 40's and 50's century. Many natural products are being discussed in this review that focuses on different targets, like anti-bacterial natural products in which different antibacterial agents from natural sources is being discussed with brief discussion on plant *Hyssopus caspidatus.* Many more activities is being discussed in this review like antifungal, anti-tumor, anti-diabetic, anti-malarial in which their mechanisms and their suitable example is described in this review.

***Keywords*:** Natural products, Antibacterial agents, Anti-tumor agents, Anti-diabetic agents, Anti-malarial agents.

Introduction

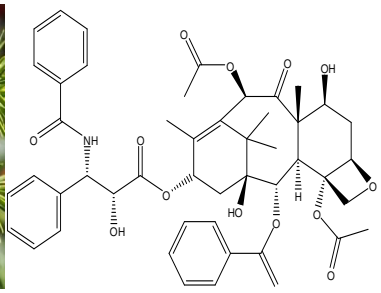
The most emerging field in the application and uses of medicines and drugs are the Natural products, with the wide range of biological activities having multiple uses in diverse fields (1). From 1950s to 1960s, it is considered as the golden age of the discovery of the natural products (2). Taking consideration, the therapeutic power of the natural products, many studies are being going on through which many bioactive compounds are being discovered every year that leads to further investigation on the isolated compound (3). As their wide range of biological use they have multiple origination i.e; from bacteria, fungi (secondary metabolites), plants and animals. The products of secondary metabolism are used because they do not require live host in the laboratory (4). The collection of natural products provides the high range of stereochemistry and very wide range of pharmacophore, this ability provides hits even against very difficult targets, e.gprotein-protein interactions (5). Natural products from plant source like morphine and paclitaxel have many therapeutic activities in medicinal field (6).

Papaver somniferum



Morphine

Taxus brevifolia



Paclitaxel Structure

Fig. 1 : Two most successful examples of natural product in medicinal field (6)

The discovery of the natural products isproven to be useful as herbicides, pharmaceuticals and various insecticides (7).The roots of the finding discovery of the natural products are way longer than 75 years ago with the discovery of penicillin in which more than 23,000 natural products were considered to be active compounds those were produced from bacteria, belongs to family *Actinomycetaceae,* which further leads to advancement in the natural product industry with the discovery of streptomycin at Rutgers university in 1940s in many countries (8).Microbial origin natural product is being privileged in the circle of development of antibiotic. Nevertheless, highly succeeding synthetic antibiotics have proven to be very effective as therapeutic agent and hence to be continued to use, majorly those antibiotics are based on natural product synthesized like, sulfa drugs, oxazolidinones. Later 1000 novel natural products were discovered by different laboratories worldwide (9).

The advancement in the field of natural products is the large range of molecular weights along with their complexities. Natural products are optimized evolutionarily similar to drug type molecule and stayed the supreme sources

of drug and their leads. Many tests were carried out to check the biological activities in context of microbiology, chemical engineering, isolation and identification of the antibacterial and antiviral acting natural products (10).

Till date many studies and discoveries were done on the natural products as the advancement in this field worldwide (11).

Advancement of natural products

In the last 30 years, there is notable increment of 50% in the natural products and natural products inspired NCEs (new chemical entities) (12).During 2008-2013, 25 new chemical entities among which 50% were natural products were approved for use by US Food and Drug Administration (13). In 2013, 1453 NCEs were discovered among which 40% were natural products were approved(14). Natural products are classified differently according to their sources, biological function, biosynthetic pathway. Altogether there are 326,000 molecules of natural products discovered till date (15).

Natural product approach to drug discovery

Many natural sources of medicinal extract component work in many collaborative manners to perform therapeutic effect in a counterproductive manner by isolating the single component (10). It can be further illustrated by the below mentioned flow chart;

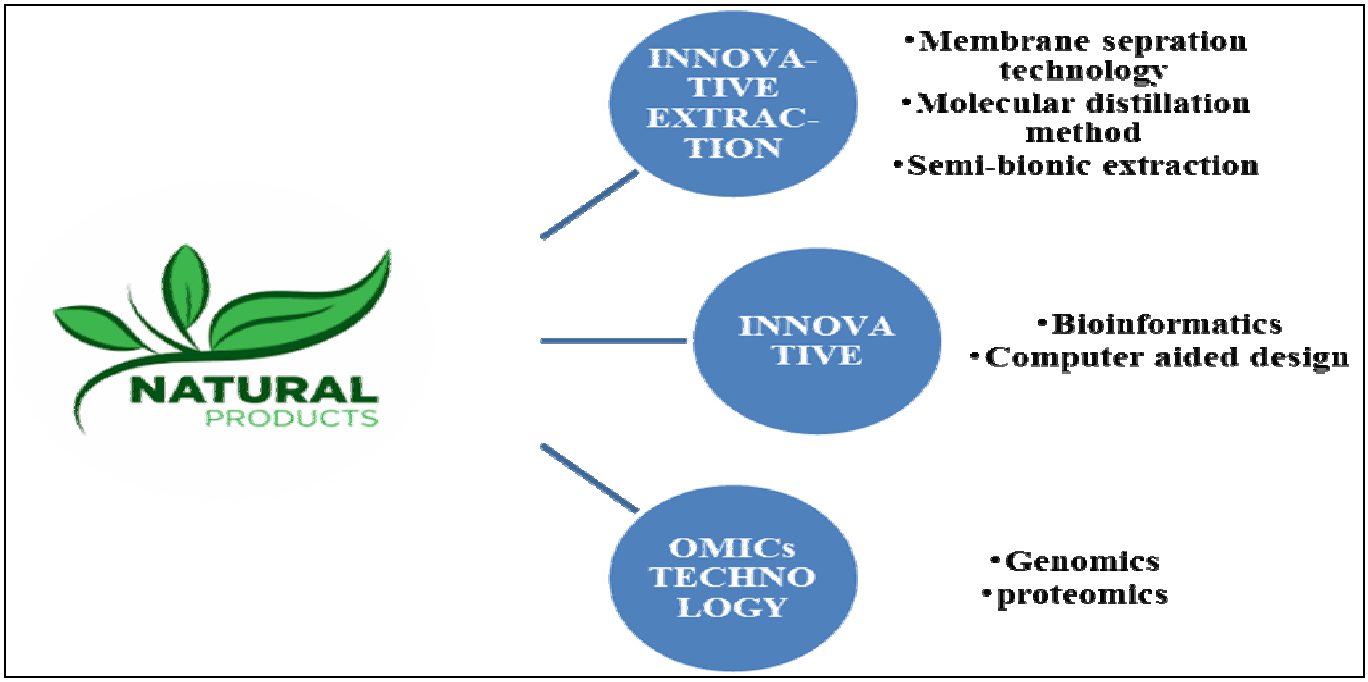


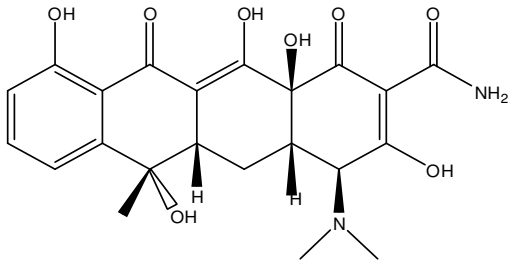
Fig. 2 : Innovative technology for natural product drug discovery (10)

Natural products as pharmaceutical drugs

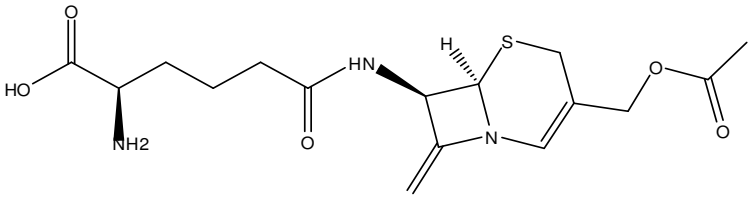
1. **Antibacterial agents** – The most important pharmaceutical use of natural products is in the antibacterial treatment. Plants always played a sole role as the prevention of infectious diseases all around the world (16). Thousands of natural products along with their second and third generation derivatives are being continuously used in the treatment of the gram-negative and gram-positive infections of bacteria in animals and humans (17). Generally used semi-synthetic derivatives of antibacterial agents in the treatment of respiratory infections and skin infections are the azithromycin, clarithromycin, doxycycline, amoxicillin and cephalexin (18). Tylosin along with its derivative tilmicosin used in the treatment of bacterial infections in animals.

Antibacterial agents that is related to the erythromycin and tylosin, they behave as translational inhibitors by blocking the nearly polypeptide chain and at distant position in case of tetracycline and binding to ribosomal subunit 50s and act as bacteriostatic for the pathogens (19, 20).

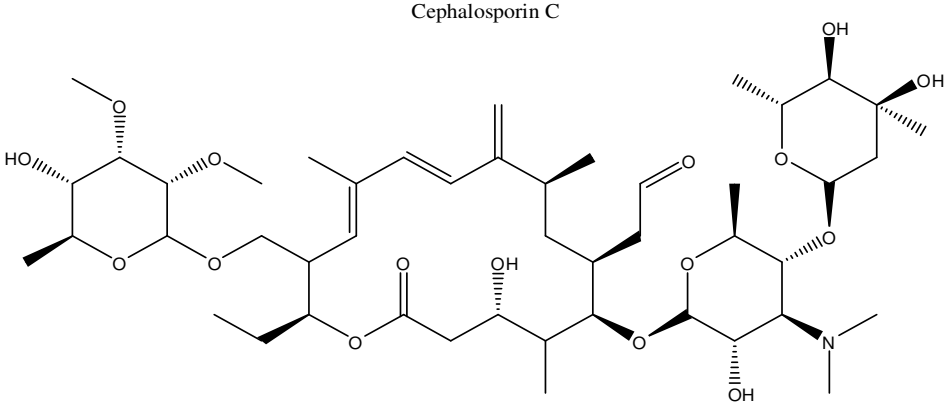
Some of the antibacterial natural products are not used clinically because of their rarely observed side effects, like chloramphenicol which is very active and potent against gram-negative bacteria (21). Different types of plants are also used as medicines or in food as additives to reduce the adverse effect due to oxidative stress and free radicals. Among which one is *Hyssopus caspidatus*, belongs to family *Lamiaceae*. Many chemical compounds have been investigated until now as essential oils of *Hyssopus caspidatus*. To check out the biological activity and the essentiality of *Hyssopus caspidatus* the considered species is the *H. seravshanicus* from Tajikistan and isolated almost 17 compounds. The main metabolites of this plant was found to be phenolic compounds, which act as potent antioxidant and have the potency to increase the content of melanin (22).



Tetracycline



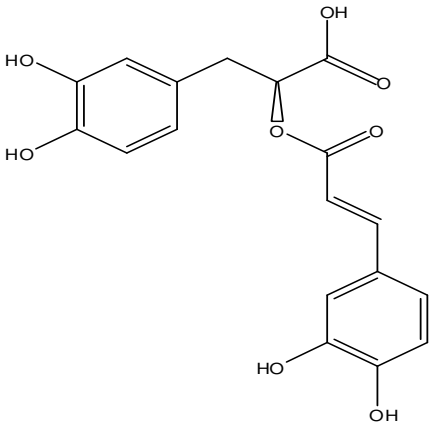
Cephalosporin C



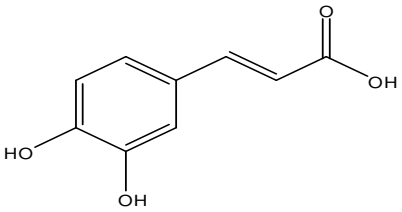
Tyrosin

Fig. 3 : Structures of antibacterial as natural products (21)

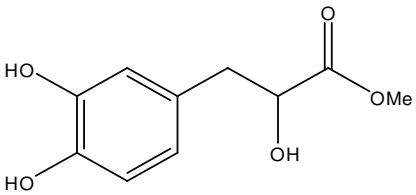
The isolated structures were done by combining different types of silica gel and the structures were confirmed by spectroscopic data.



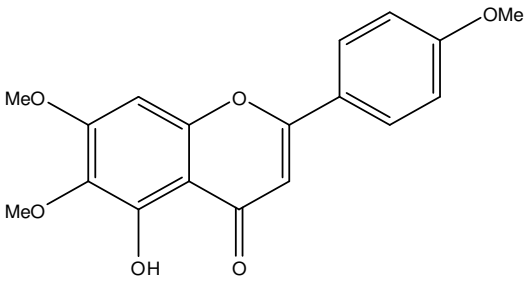
Compound 2



Compound 6



Compound 5



Compound 9

Fig. 4 : Isolated compounds of *H. cuspidatus* (23)

Among the above isolated structures, the most abundant structures were of Methyl rosmarinate (1) and rosmarinic acid (2) (23)

Antioxidant activity –

a) Highest value Compound 6 (IC50 = 24.68 ± 2.14 lM) and Compound 2 (IC50 = 30.32 ± 2.38 lM)

b) Lowest value Compound 3 (IC50 = 11.47 ± 6.51lM)

Antibacterial activity – a) highest activity Compound 5 (9.5 mm), 9 (7.5 mm), and 16 (7.5 mm)

b) Lowest activity Compound 2 (6.2 mm)

2. **Anti-fungal natural products** – The occurrence of resistance to antifungal agents is increasing continuously in past years, hence the need for new antifungal has also increased (24).The emergence need for new antifungal agents are in demand because of resistance developed by already existing agents (25). A wide range of fungal infections varies from the superficial condition of nails and skin to life-threatening diseases (26).The therapeutic availability for the fungal infections is being broadly classified into two classes: polyenes and azoles (45). In many recent researches, the study is being reported on phenolic compounds antifungal activity from natural sources (27). As anti-fungal natural products act in two different families for the treatment in humans i.e; echinocandins (amphotericin B and nystatin) and polyene macrolides (caspofungin) both act differently, one by creating holes in the fungal walls and the other one is by inhibiting the formation of the enzyme glucan synthase by the fungal cell wall (6,28).

Antifungal compounds derived from plants- Plants are the sources that have unlimited ability for the synthesis of aromatic compounds with different functional groups, the main compounds are phenols and their oxygen derivatives (24). *Candida albicans* is the most dangerous fungal infection, azoles are the most effective class of antifungal to treat (29), resistance to already existing antifungal led to discovery of new antifungal that leads to the study of various saponins among which some has shown positive results (30,32).One of the resistance identified in candida species is the point mutation in ERG11 (31). Five stages are being decribed below;

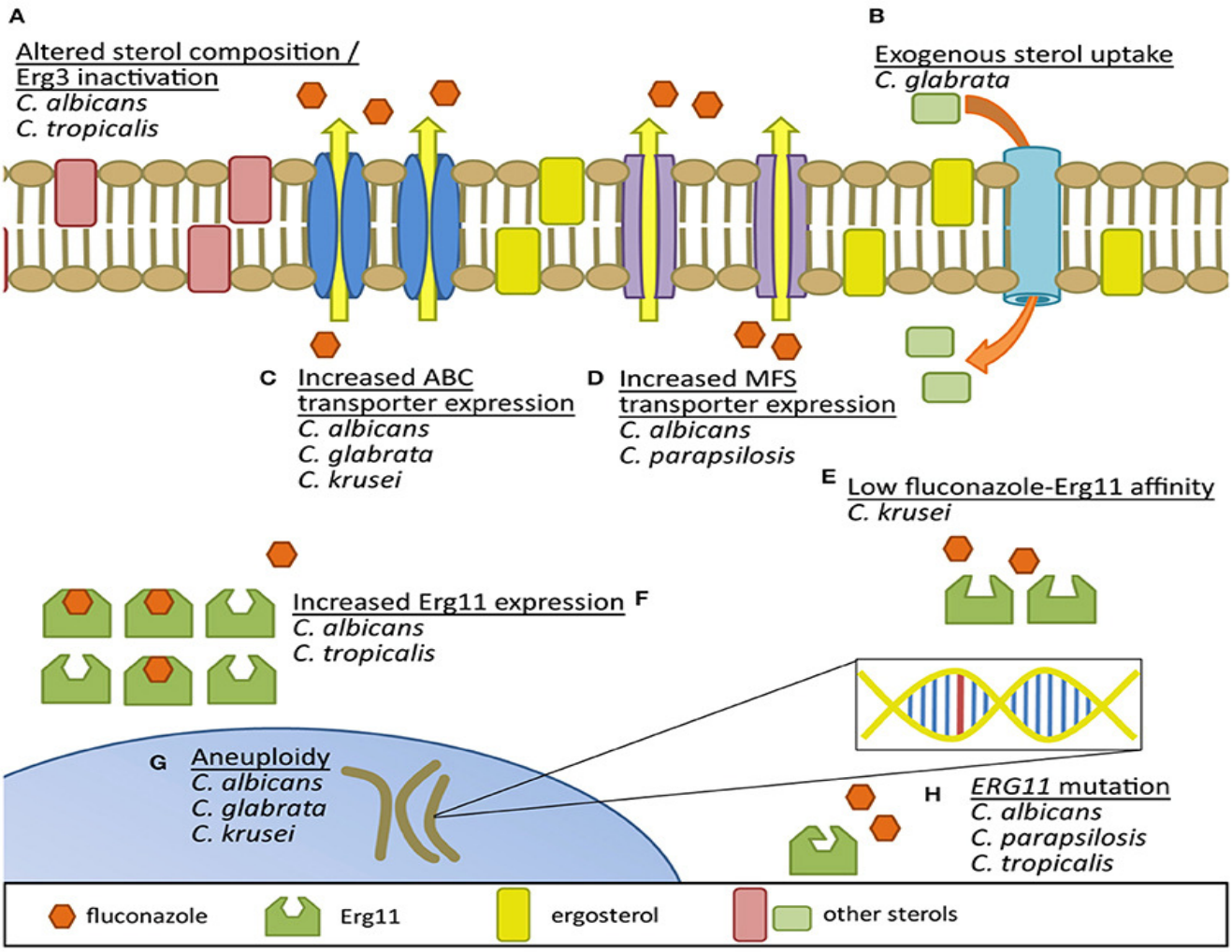


Fig. 5 : Azole resistance in five different stages (29)

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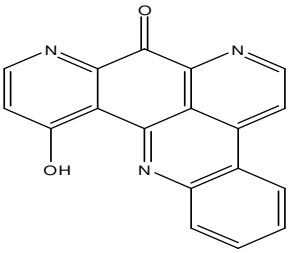
Targets for many antifungals is the ergosterol synthetic pathway, that converts acetic acid into ergosterol (33). Biofilm related infections are also associated with most common fungi *Candida albicans* (34).

Altogether, *C. albicans* is the member of human microbiome only, it stays inside the host lifelong and is harmless but in some circumstances, it proves to be life-threatening to human (35).

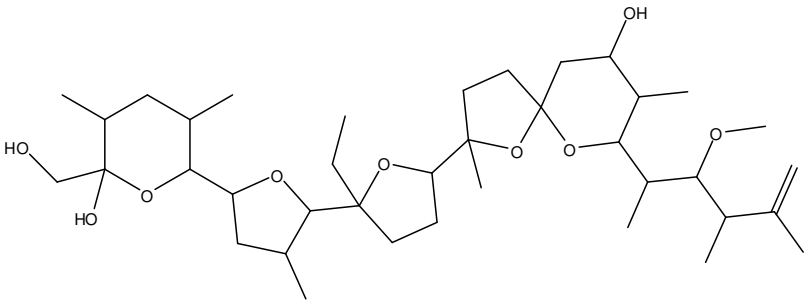
Infections due to *Candida* species:

- AIDS patients mostly develop oropharyngeal Candidiasis (malnutrition and interfere in the ADME of body) (36).
- Vulvovaginal Candidiasis (women with type II diabetes mellitus) (37).
- Ocular Candidiasis (e.g. Intubation, delirium) (38).
- Oral Candidiasis (endogenous organism responsible for the infection in the host body) (39).
- Mammary Candidiasis (it may be because of albicans or non-albicans) (40).

Among all the species of *Candida*, the most prevalent one is *Candida albicans* (50.7%), *Candida Parapsilosis* (17.4%), *Candida glabrata* and *Candida Tropicalis*, which constitutes almost (16.7% and 10.2%). The main affected person is of mean age of 50-54. (41, 42). Some of the agents that are active against fungal infections from natural sources are been shown below; (43, 44)



Meridine

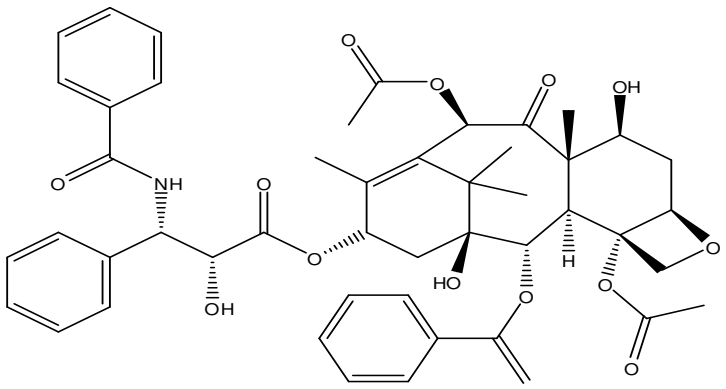


Monensin

3. **Anti-tumor natural products** – A very wide range of natural products act against tumor effect, anticancer agents to be of natural sources or related to exhibits 60% of the total agents (54), the most effective and way ahead to be discovered agents exists in marine sources (46, 49). One of the example of plant source that well act for the cancer treatment is Vinca alkaloid that isolates from *Catheranthus roseus*, the most active agent of vinca alkaloid is vincristine, its use was increased with its positive role in Hodgkin's disease (47), followed by etoposide that was used in the treatment of testicular cancer used along with bleomycin (48) and it also participates in intracellular redox cycle reactions (53). The effective method for discovering the drugs of chemical prototype is bioactive guided fractionation that is considered to be effective for human and more yet to be discovered (50). Cancer cells produce very high level of reactive oxygen species, which leads to increment of basal oxidative stress in the body (51). The high level of basal oxidative stress can be reduced with the use of pro-oxidants that targets tumor cells that inhibits the cells to not be vulnerable to different agents (52, 55). More than 50% of agents with modified structure are under clinical trial for the anticancer activity like romidepsin, ixabepilone, dibenzodizepine (ECO-4601) (54).

Effective anticancer agents: Natural products and their derivatives had been proved effective in health care and promotes 50-60% of their use in anticancer agents (56), some of them are described below;

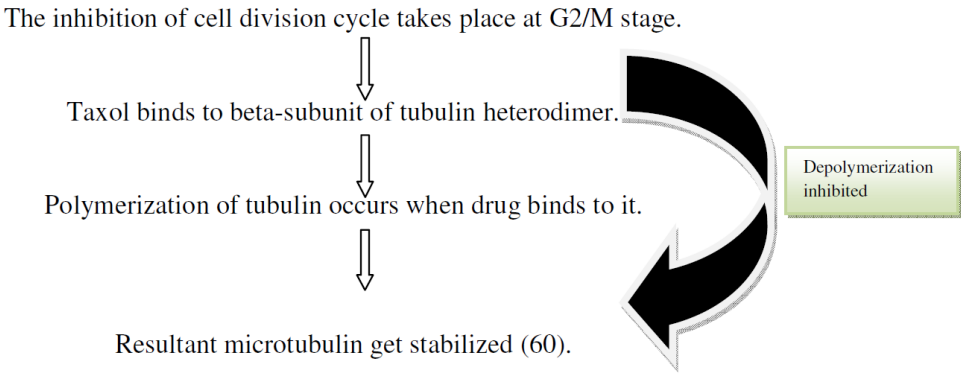
Taxol- It is naturally occurring complex polyoxygenated diterpenoid, isolated from the bark of tree pacific yew (57). Its use was approved and increased for ovarian cancer and breast cancer in 90's, but now onwards Taxol is produced semi-synthetically also due to less production by only natural source (58).



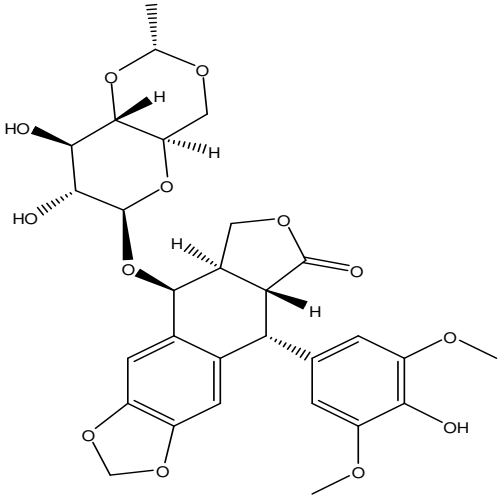
Paclitaxol

It is clinically used for many types of human cancers and used in combination with other anticancer agents in chemotherapies, like cisplatin, riboflavin, carboplatin (59).

The inhibition of cell division cycle takes place at G2/M stage.



Podophyllotoxin- It is naturally occurring bioactive lignan, isolated from the roots of *p. emodi* (61). Its use was approved with the cure of venereal warts. Some derivatives of podophyllotxin is used as anti-cancer, anti-arthritis, anti-wart extensively is etoposide and teniposide (62).



Etoposide

It is clinically used in the treatment of lung cancer, lymphomas, non-hodgkin's, genital tumor. But above all the therapeutic use, due to some side effects of gastrointestinal and high toxicity it is being limited for clinical use (63). With few structural modifications, its toxicity effect is being overcome (64).

Prevention of spindle formation by inhibiting the tubulin assembly into microtubules.

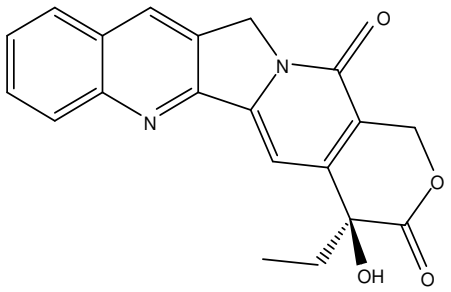
Stabilization of enzyme DNA complex

Blockage of DNA topoisomerase II

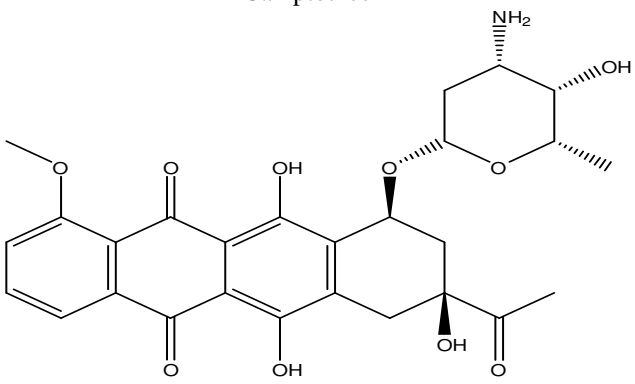
DNA is cleaved and linked to enzyme covalently (65).

Camptothecin- It is naturally occurring pentacyclic alkaloid, isolated from tree of love (Camptotheca aluminata) (66). It belongs to one of the promising class of anticancer agents (67), its derivatives are used in the treatment of solid cancers because of its highly toxic nature and mainly insoluble like topotecan and irinotecan (68, 69).

The most promising target of Camptothecin is found to be topoisomerase I.



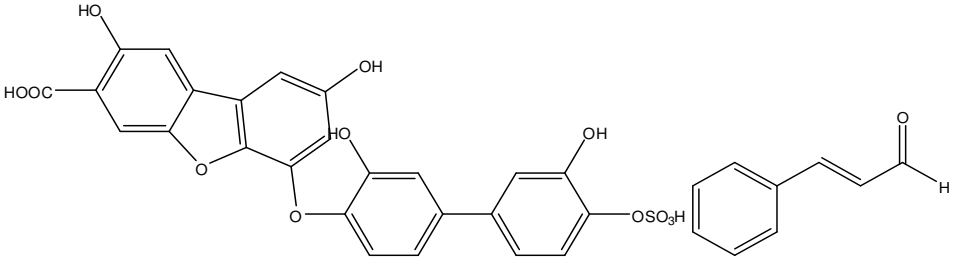
Camptothecin



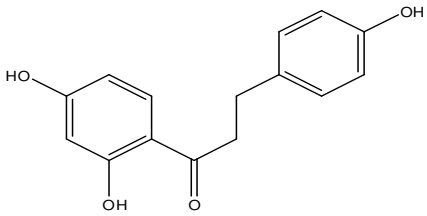
Doxorubicin

4. **Anti-diabetic natural products –** The most hazardous and complex disease arising is diabetes mellitus (most affecting disease in patients). There are generally many forms of diabetes that includes Type 1 (insulin dependent) and Type 2 (insulin non-dependent) diabetes. Among Type 1 and Type 2 most commonly seen diabetes in patients is Type 2 (rate rises every year). There are many treatments already existed for diabetes that suits to patients but not to all the patients, includes extracts from plants i.e.; as natural products.

Anti-diabetic natural products from plant extracts – there are many plant extracts that act as anti-diabetic agent, the natural products that inhibits protein tyrosine phosphate is lignans (vanillic acid derivatives, cinnamaldehyde), the natural products that inhibit aldose reductase is flavanoids (davidigenin), terpenoids, etc. (71)

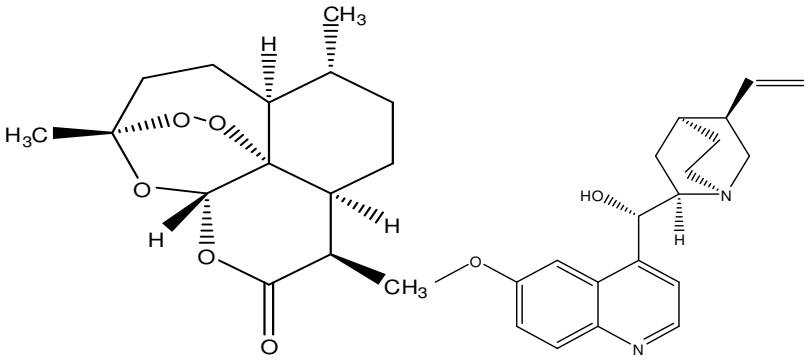


vanillic acid cinnamaldehyde



davidigenin

5. **Anti-malarial natural products –** Malaria is an infectious disease that is most commonly seen in tropical countries, if not treated properly it is life threatening for affected patients. From many past years natural product natural agents were in use and contributed well treatment in malaria but later replaced by synthetic derivatives. As natural products are never ending synthesis agent for many diseases it comes into treatment once again with many of their already existing derivatives to overcome the drawbacks for its withdrawal. Some of the effective anti-malarial natural products are artemisinin, quinidine. (72)



Artemisinin quinidine

Conclusion

As already discussed, natural products have therapeutic activities because of their complex structures. As a means to produce novel natural product at combinatorial biosynthesis due to less knowledge about the need of structure of natural product. Further the combinatorial biosynthesis may be combined with the medicinal chemistry to increase the number of compounds used for evaluation. In this review we have covered the various biological properties of the natural products like antibacterial, antiviral, antitumor and in detail the antibacterial activity by taking *Hyssopus caspidatusas* the plant extract and taking its isolated compounds for their antioxidant and antibacterial activity, and about different antifungal and antitumor agents and their role as natural pharmaceutical agent. As there are many advancement and increment in the field of natural product due to their various biological activity and therapeutic activity, the curiosity to know more about the use and application of natural products in humanly needs, it will further increase and the progress as shown in last few years will continue growing positively.

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