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An overview of plant secondary metabolites, their biochemistry and generic applications

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ABSTRACT

Plants are a source of a large number of secondary metabolites. Secondary metabolites are associated with exclusive subordinate functions ranging from defense to adaptive behavior. Their absence does not necessarily hamper the growth of the organism. However, they enhance their chances of survival against environmental stress. Many plant secondary metabolites are unique sources of active pharmaceutical compounds, flavours, anti-oxidant supplements, cosmetic products, anti-cancer agents, and food additives. This has resulted in great interest in large-scale production and enhanced extensive researches for commercially valuable plant secondary metabolites. Many plant-based drugs are available in the market such as Vinblastine, Tubocurarine, Reserpine, Paclitaxel and Asiaticoside. The article classifies various secondary metabolites on their discrete chemical structure and biological synthesis pathway. It further elaborates on their biological roles and explores their close association with primary metabolites. Additionally, this article further provides an insight into the biochemistry of various prominent secondary metabolites.

Keywords: Plant secondary metabolites, Classification of secondary metabolites, Biosynthesis of secondary metabolites, SDM.

INTRODUCTION

The organic compounds in principal metabolic pathways with direct influence on growth, development, and reproduction in cellular organisms have been termed as primary metabolites. These metabolic intermediates and products are widely distributed all over the biosphere since they play a crucial role in physiological activity by governing the static and dynamic actions of an organism's metabolism. Secondary metabolites, in contrast to primary metabolites; are not directly involved in principal metabolic activities but are associated with a wide range of subordinate functions such as defence and interaction with other organisms that ultimately increases their chances of survival.

Secondary metabolites are modifications of primary metabolites and often result of extended primary metabolic pathways. For example, pyruvate, a product of glycolysis forms intermediate Acetyl CoA that undergoes mevalonic acid pathway and yields terpenoids. Similarly, phosphoenolpyruvate. which is intermediate of glycolysis pathway undergoes Shikimic acid pathway resulting in synthesis of alkaloids.

Few secondary metabolites are good alternatives for synthetic drugs. The presence of these compounds may potentiate or synergize the effect of other compounds in medicine [1]. Many phytochemicals are used as food additives, flavour, and other raw industrial material in addition to their therapeutic purpose [2]. Many plant and bacterial secondary metabolites have been found to exhibit antiviral, antibacterial, and antifungal effects and thus used in modern medicine. For example, polyphenol undergoes chemical transformation by normal gut flora and taken up through enterocytes. It exhibits antibacterial effect up to a certain concentration in the blood [3]. Morphine, an alkaloid derived from opium poppy is known to exhibit strong analgesic effect. Some phyto-secondary metabolites like Taxol inhibit the formation of microtubules and thus hamper the rapid cell division hence utilized in the preparation of anti-tumour drugs.

Numerous secondary metabolites are produced during the growth phase of plant. Plants produce secondary metabolites to survive fluctuating environmental conditions. The rate of production of secondary metabolites in different phyla is influenced by geo-climatic, seasonal changes, surrounding temperature, light, humidity, and developmental process among others. Although, secondary metabolites increase the chances of survival against odd environment, Secondary metabolites do not directly influence plant's physiological process. However, Secondary metabolites may involve in the production of complex chemicals that ultimately contribute to the structural and functional stabilization. Many plant secondary metabolites are responsible for shade and colour of petals thus increases their chances of pollination by attracting insects and birds. Plant also utilises secondary metabolites to prevent spread of

infection form one part to the other. Many volatile secondary metabolites also attract pollinators. These secondary metabolites also attract herbivores for seed dispersion. Some secondary metabolites are shown to prevent pathogen induced cancer in plants.

Secondary metabolites are associated with environmental adaptive behaviour in plants. Although the absence of secondary metabolites in plant does not cease growth and reproductive cycle but may affect the survivability in long run. Plant secondary metabolites are classified into four broad categories i.e. terpenes, phenolics, glycosides, and alkaloids. Secondary metabolites in microorganisms play a crucial role in the establishment of interactions with other ecological organisms including plants. Microbial secondary metabolites have distinctive chemical structures and their synthesis is governed by special regulatory mechanism. Synthesis of secondary metabolites is initiated in stationary phase [2]. This might be the result of responses to the environmental pressure faced during stationary and decline phase. Many fungal secondary metabolites are the result of complex epigenetic modifications and are responsible for the conservation of their distinctive genetic makeup [3].

Classification

Secondary metabolites can be classified based on their chemical structure, composition (presence or absence of nitrogen or hydroxyl group) or their solubility in various solvents or the more conventional method; based on their biosynthesis pathway.

Plant secondary metabolites are classified into four major groups based on their chemical structure: terpenes, phenylpropanoids (i.e. phenolics), polyketides, and alkaloids [4]. They are also classified into terpenes (with formula $(C_5H_8)_n$), terpenoids (oxygenated terpenes), phenolic compounds (characterized by the presence of hydroxyl group), Alkaloids (Nitrogen-containing), and Sulphur containing compounds. Conventionally secondary metabolites are classified into terpenes, phenolics, phytosterol (plant steroids), alkaloids, and flavonoids (polyphenolic) [5].

Terpenes

Terpenes are unsaturated hydrocarbons mainly produced by Coniferophyta. The oxygenated forms of terpenes are referred as terpenoids. They are major constituents of many essential oils. Terpenes and terpenoids jointly comprise 55,000 entities [6]. Seventeen plant species have been found to carry genes to encode the terpenoid synthase enzyme which is essential for the biosynthesis of terpenes [7]. Terpenes are the most widely distributed class of plant secondary metabolites. Various terpenes have a wide range of functions including defense against herbivores, resistance to diseases, plant communication, and attraction of pollinators [8]. Their role as plant hormones (Abscisic acid, gibberellin) is perhaps the most exploited aspect of plant tissue culture.

Biosynthesis of terpenes

The synthesis of terpenes is carried out by two principal pathways, Mevalonic acid (MAP) pathway and 2-C-Methyl-D-erythritol 4-phosphate (MEP/DOXP) pathway. MAP pathway for the synthesis of terpenes begins with Acetyl-CoA molecule released from tricarboxylic acid cycle. MAP pathway is a part of HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase) pathway. While, pyruvate acts as a precursor for the synthesis of terpenes through MEP pathway.

Table 1: Classification of Terpenes

Terpenes	Number of isoprene unit	Number of carbon atom
Monoterpenes	2	C_{10}
Sesquiterpenes	3	C_{15}
Diterpenese	4	C_{20}
Sesterpenes	5	C_{25}
Triterpenes	6	C_{30}
Tetraterpenes	8	C_{40}
Polyterpenes	>8	$>C_{40}$

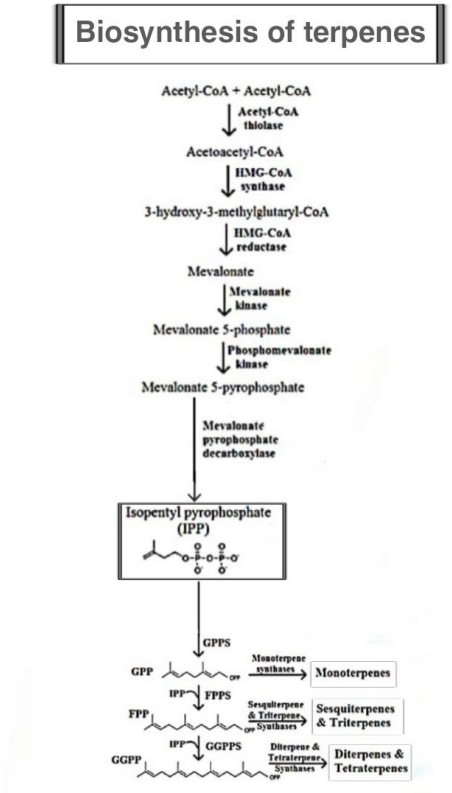

Figure 1: Biosynthesis of Terpenes

Plant phenolic compounds

Plant phenolic compounds are synthesized through shikimate, pentose phosphate, and phenylpropanoid pathways. These phenolic compounds are usually produced in response to ecological pressures such as pathogen, insect attack, Ultraviolet (UV) radiation or wounding. They carry benzene rings, with one or more hydroxyl substituents, and range from simple phenolic molecules to densely polymerized compounds. Many phenolic compounds are present in leaves and discourage herbivores [9].

Phenolic compounds are mostly found in vascular plants i.e. Lycopodiophyta, Pteridophyta, Gymnosperms, and Angiosperms (flowering plants or Magnoliophyta). They are also found in non-vascular plants such as bryophytes in a meager extent. Phenols are released into soil during the decomposition of dead plant parts. Although, throughfall by living plants also significantly contributes to the soil phenolic content that ultimately leaves the ecosystem as dissolved organic carbon. This soil phenolic content can also be absorbed into clay minerals. A phenolic compound in the soil might form chelates with aluminum or iron ions [10]. Generally, phenolic

secondary metabolites are classified into Simple phenolics, Tannins, flavonoids, coumarins, stilbenes, lignans, chromones, and xanthones.

Flavonoids

Flavonoids comprise the largest family of plant phenolics. The majority of flavonoids are found in higher plants. A significant amount of flavonoids are found in Polygonaceae, Rutaceae, Leguminosae, Umbelliferae, and Compositae [11]. Flavonoids contribute to a wide range of subordinate functions such as protection against UV radiation. Major flavonoids include chalcones, aurones, flavones, flavonols, flavanones, isoflavonoids, leucoanthocyanidins, anthocyanins, and catechins.

Biosynthesis of plant phenolic compounds

A significant amount of plant phenolic compounds is synthesized through the pentose phosphate pathway, Shikimate pathway, and phenylpropanoid pathway. Newly synthesized aromatic amino acid phenylalanine acts as a precursor for the synthesis of phenolic compounds (including phenol-containing amino acids).

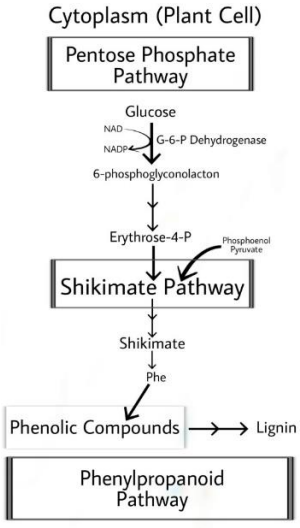

Figure 2: Biosynthesis of phenol compounds in plants through various pathways

A glucose moiety is utilized in pentose phosphate pathway (PPP) in which irreversible conversion of glucose-6-phosphate into ribulose-5-phosphate takes place. This process is catalyzed by the enzyme glucose-6-phosphate dehydrogenase (G6PDH). This conversion produces equivalents of nicotinamide adenine dinucleotide phosphate (NADPH) for cellular anabolic reaction. PPP also yields erythrose-4-phosphate [12]. This moiety along with phosphoenolpyruvate generated from other sources is utilized in the Shikimic pathway to generate phenylalanine which is further utilized to produce phenolic compounds which include wide verities of substances such as simple flavonoid, complex flavonoids, phenolic acids and colored anthocyanins [13].

Alkaloids

Alkaloids are pharmacologically active, nitrogen containing plant secondary metabolites. Alkaloids generally occur in plant as a salt of organic acids. Few alkaloids are found to be glycosides of sugars and esters of organic acids. Some of the widely known alkaloids include caffeine, morphine, nicotine, quinine, cocaine, strychnine, and solanine.

Their biological role is not fully clear but most of the alkaloids are considered to be involved in defensive role. For example, aporphine produced by *Liriodendron tulipifera* protects it from parasitic fungi. However, most of the animals are adapted for the consumption of common alkaloids [14].

Biosynthesis of Alkaloids

Most of the alkaloids are synthesized from amino acids such as lysine, tyrosine, and tryptophan. Alkaloids are synthesized by a wide range of complex mechanisms. Due to the numerous complex mechanisms, they are not easily classified. Further research is needed to categorize them systematically based on their biosynthesis pathways [15].

The reaction of amines with aldehyde or ketone yields Schiff bases. These reactions are involved in the biosynthesis of alkaloids.

Phytosterols

Phytosterols are plant steroids characterized by hydroxyl group present at C-3, and highly branched C-17 carbon. They are universally present in all higher plants. They have both structural as well as dynamic roles in plants. Research suggests that many phytosterols possess antioxidant activity, anti-inflammatory activity and anti-cancer activity [16]. phytosterols are found as free sterol and in conjugated forms such as esters, steryl fatty acid, steryl phenolates, steryl glycosides, and acylated steryl glycosides [17]. Major phytosterols such as sitosterol, campesterol, and stigmasterol regulate membrane fluidity and permeability of plant cells [18].

Biosynthesis of Phytosterols

The two principal pathways for most commercially valuable phytosterols include cytosolic and plastidial pathways. Acetate–mevalonate pathway occurs in the cytoplasm and the mevalonate-independent pathway occurs in the plastid. Cycloartenol synthesized through cycloartenol synthase acts as the committed precursor for phytosterols. The generic pathway for plant sterol biosynthesis is through either cycloartenol or lanosterol [19].

Quinone

Quinones are secondary metabolites that arise from the metabolism of benzene, phenol and other aromatic compounds. They are one of the most pharmaceutically exploited plant secondary metabolites [20]. Quinones form major classes of cytotoxins which are used for cancer therapy [21]. Most widely distributed quionons are benzoquinones, naphthoquinones, anthraquinones, and polyquinones. Ubiquinones and plastoquinones are bezoquinone while Menaquinones are napthoquinones. Ubiquinones constitute a part of the respiratory chains of eukaryotic mitochondria while, plastoquinones are components of photosynthetic electron transport chains in plant chloroplasts. Phylloquinone K1 is a phytyl naphthoquinone that has a prominent function in the photosynthetic electron transport in photosystem I [22]. Recent researches have revealed the role of quinones in the regulation of gene expression and signal transduction [23].

Biosynthesis of Quinones

Tyrosine acts as a precursor for the synthesis of homogentisate (HGA) while prenyl chain is formed in non-mevalonate pathway [24]. The condensation of these two is catalyzed by enzyme homogentisate solanesyl transferase. Condensation is followed by methylation.

Synthesis of quinones usually occurs in the chloroplast membrane. But recent researches indicated endoplasmic reticulum and gogli apparatus membranes are also the site for the synthesis of quinones [20].

Bioactivity

Antimicrobial activity

Antibiotic resistance in microorganisms is not an uncommon phenomenon. This has become a concerning subject for the scientific community. A lot of plant based herb preparations are part of traditional knowledge in many indigenous communities all over the world. The emphasis on the discovery of antimicrobial components paved the path for researches on pharmaceutically anti-bacterial and anti-fungal compounds [25].

Terpenes

Terpenes extracted from the bark of the plant exhibit anti-bacterial activity against *Streptococcus faecalis*, *methicillin-resistant S. aureus* (MRSA), and *P. aeruginosa* [26]. Leaf ethanol extract of *Morinda citifolia* contains a significant amount of terpenoids and researchers have attributed its antimicrobial properties to its terpenoid content. This leaf extract is effective against *P. aeruginosa* and *S. epidermidis* in controlled studies [27]. Recent researches have indicated that terpenes extracted from plants of Asteraceae (daisy), Lamiaceae (mint) and Rutaceae (citrus) families are known to exhibit high antimicrobial activities [27]. Most researchers have focused on antimicrobial properties of plant extracts in various solvents hence the involvement of other phytochemicals in microbicidal activity should not be neglected [28].

Phenolic compounds

Many naturally occurring phenolic compounds discourage phytopathogens because of their antimicrobial activities. For instance, research conducted on extracted secondary metabolites from grapes and almond plants indicated antibacterial effects against gram-negative bacteria such as *Xylella fastidiosa* [29].

Flavonoids

Many investigations have revealed the synergy between existing chemotherapeutics and flavonoids [28]. Many recent types of research have focused on the antimicrobial mechanism of selected flavonoids. Flavonoids such as quercetin inhibit DNA gyrase activity. Other flavonoids such as Sophoraflavone G and epigallocatechin gallate have shown to inhibit cytoplasmic membrane function thus leading to affect energy metabolism [30]. The scientific literature reported antimicrobial effects of flavonoids in various solvents. Growth of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Enterococcus faecalis* were inhibited indicating an antimicrobial effect of flavonoid extracts in various solvents [31].

Alkaloids

Alkaloids are being used as active components of many herbal remedies for centuries. They also constitute drugs that are widely abused. Several alkaloids are cytotoxic and have the potential to cause poisoning in humans too. Several Middle Eastern plants such as *Datura stramonium, Peganum harmala,* and *Achillea millefolium* are subjected to extensively many researches[23]. The denatured alkaloids extracted from these plants are effective against many pathogens such as *E. coli, S. aureus, P. aeruginosa, K. pneumoniae* and *Proteus mirabilis* [32].

Phytosterol

Several phytosterols have potential antifungal effects and are utilized as active compounds in many anti-fungal drugs [31]. Plant sterols such as methyl dehydroabietic, brassisterol, stigmasterol and fucosterol extracted from callus culture explicitly exhibit antifungal activities [33].

Antioxidant Activity

All cellular organisms have a mechanism to prevent oxidative damage. Oxidants and free radicles are yielded from many parallel metabolic reactions as part of a normal cellular mechanism. Several scavengers and antioxidants are employed by cells to maintain a healthy balance between free radicles and scavenging antioxidants. But excessive production may lead to oxidative stress which might damage lipids, proteins, and DNA. Many synthetic antioxidant drugs are available in the market but certain concerns have been raised due to their carcinogenic nature [34]. Therefore interest has significantly increased in seeking naturally available antioxidants.

Flavonoids as antioxidants

Flavonoids are found to be good scavengers for free radicles in vitro environments due to their capacity to neutralize free radicles and prevent the production of reactive oxygen species [35]. Their antioxidant activity is determined by their structure. The data from different researches have clearly indicated that the presence of heterocyclic ring determines their scavenging capacity since radical scavenging activity depends on attached 3-hydroxyl group [35].

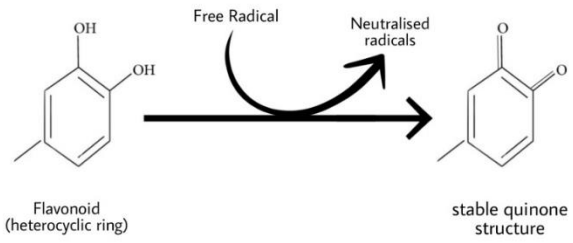

Figure 3: Scavenging activity of Flavonoid

Pharmaceutically active plant secondary metabolites and their employment in modern medicine

Phytochemicals are highly exploited sources of the plant-based drug. They have been utilized in conventional and folk medicines for centuries. These phytochemicals are also utilized in modern medicines for their antimicrobial, anti-oxidant, and anti-diabetic activity [36]. The development in genetic engineering and bioinformatics has allowed us to detect, screen-analyze, and produce pharmaceutically valuable novel secondary metabolites on large scale. The modern extraction techniques utilized for the production of plant active compounds are time and energy-efficient and do not require a large amount of raw material. In addition to this, rDNA technology is utilized to reduce toxins and increase the uniformity and predictability of desired active compounds. Utilization of analytical chemistry in techniques such as mass spectrometry supplied with or nuclear magnetic resonance (NMR) and spectroscopy capillary electrophoresis has proved an

effective tool to perform metabolome analysis of secondary metabolites allowing us to determine structure associate functions.

Alkaloids

Alkaloids such as benzylisoquinoline, papaverine exhibit the inhibitory effect of several viruses. Alkaloids extracted from *Cryptolepsis sanguinolenta* exhibit inhibitory activity of several gram-negative bacteria and yeast. Quinine is a popular alkaloid that exhibits antimalarial activity against the malaria parasite.

Table 2: Few selected alkaloids and their utilization as an isolated compound in medicine [37-54].

Plant species	Bioactive compound	Mode of action	Medical uses	References
Aconitum napellus	N-methyl-N-deethylaconitine	Activates Na^+ channel	Analgesic	Murayama M et al. (1984)
Atropa belladonna	Atropine	antagonist of mAChR	parasympathomimetic	Bettermann H *et al*. (2001)
Camptotheca acuminate	Camptothecin	inhibitor of DNA topoisomerase	tumour therapy	Chi-Shian *et al*. (2014)
Catharanthus roseus	Vinblastine	inhibit microtubule assembly	tumor therapy	Sathya *et al*. (2017)
Chondrodendron tomentosum	Tubocurarine	inhibits nAChR	muscle relaxant	Raghavendra T. (2002)
Cinchona pubescens	Quinidine, Dihydroquinidine	inhibits Na^+ channel	Antiarrhythmic	Chimienti M (1988)
Coffea Arabica	Theophylline	inhibits phosphodiesterase and adenosine receptors	Stimulant	Bucklin M Groth C. (2014)
Colchicum autumnale	Colchicine	inhibits microtubule assembly	gout treatment	Slobodnick *et al*. (2015)
Cytisus scoparius	Sparteine	inhibits Na^+ channel	Antiarrhythmic	Senges *et al*. (1974)
Erythroxylum coca	Cocaine	inhibits Na^+ channels and reuptake of noradrenaline and dopamine	analgesic; stimulant	Schuelke *et al* (1996)
Galanthus woronowii	Galantamine	inhibits AChE	Alzheimer treatment	Kim J. *et al*. (2017)
Lycopodium clavatum	Alpha-onocerin	inhibits AChE	Alzheimer treatment	Orhan I. (2003)
Papaver somniferum	Opium	agonist of endorphine receptors	analgesic, hallucinogen	Pathan and Williams (2012)
Physostigma venenosum	physostigmine	inhibits AChE	Alzheimer treatment	Howes and Perry (2011)
Pilocarpus joborandi	Pilocarpine	agonist of mAChR	glaucoma treatment	Geyer and Wolf (2006)
Psychotria ipecacuanha	Methylcephaeline	protein biosynthesis inhibitor	treatment of amebae infections; emetic	Onozawa *et al*. (2017)
Rauvolfia reserpina	Reserpine	inhibits the uptake of noradrenalin into postsynaptic vesicles	hypertonia treatment	Fife *et al*. (1958)
Sanguinaria Canadensis	Sanguinarine	DNA intercalator	Antibacterial	Croaker *et al*. (2016)
Taxus brevifolia	Paclitaxel	inhibits microtubule disassembly	tumour therapy	Tasiu (2015)

Terpenes

Terpenes exhibit wide range of activities against cancer, malaria, inflammation, and infectious diseases. Terpenoid-derived drugs are utilized as a preventive agent against a wide range of viral and bacterial infections. For instance, *Cannabis sativa* and *Eucalyptus microcorys* exhibit antitumor activity against cancer hence utilized as the active compound in many anti-cancer drugs [55].

Table 3: Different types of terpenes and their utilization in medicine [53-56]

Plant species	Bioactive compound	Medical use
Centella asiatica	Asiaticoside	Wound healing, increases circulation
Citrus sinensis	Limonene, Alpha-Pinene	Treat malaria, treat bacterial infections and migraines
salvia miltiorrhiza	Miltirone	Anti-inflammatory, cardiovascular diseases

Plant Secondary Metabolites as Anti-Cancer Agents

Cancer is a multistage process in which cells undergo uncontrolled cell division resulting in the accumulation of a mass of infected tissue. Synthetic chemicals used in cancer therapy are known to cause harm to healthy cells therefore more emphasis is given to naturally occurring anti-tumor agents. Many plant secondary metabolites such as alkaloid, diterpene, triterpene and polyphenolic compounds have shown great potential to be anti-cancer agents in recent studies. Researches have shown that the cytotoxicity of certain secondary metabolites can be targeted against infected tissues in cancer therapy. Some secondary metabolites have the potential to perform this role but they are not used in cancer therapy due to limited bioavailability. Some plant secondary metabolites are found to be toxic to normal human cells but have great potential to fight against a tumour. Their toxicity can be reduced by inducing chemical modification in their structure thus they might be utilized as anti-cancer drug [57].

Plant secondary metabolites are subjected to extensive research for their anti-tumor properties. Many anti-cancer drugs in market contain

plant secondary metabolites as active ingredients. Paclitaxel otherwise known as pseudo-alkaloid is a plant secondary metabolite that is isolated from *Taxus brevifolia Nutt.* It is one of the most widely used anti-cancer drug in chemotherapy. Paclitaxel contains "taxane" ring system which is consisted of a complex 6,8,6-tri-cycle-fused skeleton. This taxane ring structure is conjugated with four-member ring oxetane ring which has ester, alcohol, ketone and amide, functional groups. Although paclitaxel is an excellent anti-cancer drug, its usage is subjected to multidrug development resistance (MDR) [58].

Triterpenes such as Betulinic acid have shown a good selective index for cancer over healthy cells in research [59]. These triterpenes exhibit anti-tumour activity by inducing direct regulation of the mitochondrial apoptosis pathway. This is usually done by increasing permeability of mitochondrial membrane resulting in leaking of factor cytochrome c into cytosol and simultaneously downregulating Bcl-2 family members and inducing nuclear translocation which ultimately leads to apoptosis.

Curcumin found in turmeric powder (extracted from *curcuma longa* L.) is an orange-yellow crystalline lipophilic phenolic substance. Rhizome of turmeric contains 2-5% of curcumin and is used in Chinese and Indian traditional medicines. The use of turmeric powder has been attributed to health benefits including anti-inflammatory, anti-oxidant and chemotherapeutic activities. This could also be linked to the low rate of gastrointestinal mucosal cancers occurrences in south Asia due to regular use of turmeric in the diet [60]. A large number of data from in vitro studies have favored the effectiveness of curcumin as an anti-cancer agent [61]. Recent researches have revealed the modulation mechanism of curcumin against malignant cells. Although curcumin modulates varieties of pathways to induce apoptosis in target cells; it has an insignificant cytotoxic effect on a normal cell. These modulation mechanisms include: arresting cell cycle at G1, S phase and G2/M phase, mitochondrion polarization and caspase activation, promotion of autophagic cell death, the elevation of transcriptional factor nrf2 level through mitochondrial activated protein kinase (MAPK) signaling pathway and Akt pathway [62] and inhibition of angiogenesis downregulating PGDF, VEGF, FGF expression and inhibition of tubulin polymerisation [63].

Utilization Of Plant Secondary Metabolites As Covid-19 Antiprotease Drugs

Many Secondary metabolites which exhibit antiviral properties inhibit viral replication/transcription. Several plant secondary metabolites such as flavonoids, terpenoids, and alkaloids help to inhibit viral genome incorporation into the host cell. A variety of phytochemicals have shown antiviral activities against the herpes virus, human immunodeficiency virus (HIV), influenza, hepatitis virus and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [64, 65]. The discovery of plant-based drugs and herbal treatments has gained popularity due to the potential adverse effects of antiviral drugs. The ability of a virus to mutate their genome and become resistant to synthetic antiviral drugs has posed difficulties to fight against viral diseases. The ongoing COVID-19 pandemic has affected the world's population.

Viruses possess DNA or RNA genome encapsulated in protein envelopes. They require the host's cellular machinery to replicate and survive [66]. Inhibiting entry, replication/transcription is one of the many strategies to combat viral diseases. For instance, phytochemicals with antiviral properties that bind to carbohydrate moiety hinder cell entry [67]. This restricts viral penetration, while some secondary metabolites directly inhibit viral replication [68]. Plant secondary metabolites can effectively interact with many organic molecules. Viral 3-chymotrypsin-like cysteine protease (3C-Like protease) is one of such protein which can be inhibited by anti-protease drugs [69]. 3C-like protease plays a crucial role in viral genome replication and polyprotein processing. This protein is essential for its life cycle. Plant-derived protease inhibitors that exhibit strong antiviral activities can inhibit Covid-19_3C-like protease [70]. Glycyrrhizin, lycorine, tanshinone and curcumin have high affinity towards protease [71]. These compounds can be considered effective Covid-19_anti-protease drugs.

SARS-CoV-2 contains two proteases, a papain-like protease (PL-Pro), and a 3- chymotrypsin-like cysteine protease (3C-Like-Pro). 3-chymotrypsin-like cysteine protease is involved in proteolytic processing during viral maturation. Chymotrypsin-like cysteine protease cleaves pp1a and pp1ab polyproteins at eleven conserved sites. Its essential role in the viral life cycle makes it a promising target for drug development against SARS-CoV-2. For instance, Griffithsin could hinder virus entry to the host cell by binding to the SARS-CoV spike glycoprotein [72]. Studies have shown that Tanshinone and Curcumin exhibit inhibitory activity against 3-chymotrypsin-like cysteine protease with minimum toxicity to healthy cells [73]. Plant secondary metabolites such as Curcumin, Capsaicin, Limonene, Thymol, Glycyrrhizin, lycorine and tanshinone may be utilized as alternatives for synthetic anti-viral drugs to fight against Covid-19 [71].

CONCLUSION

Plant secondary metabolites play a crucial role in the survivability of organisms in long term. Their biosynthesis is interlinked with primary metabolism. Although the biosynthesis of many alkaloids and phytosterol is known; further studies are needed to elucidate their biological role in organisms. The exploration of plant secondary metabolites has a paved path for pharmaceutical researches because of their antimicrobial and anticancer properties. Antibiotic resistance of antibiotics and toxicity of synthetic cancer drugs have driven researches for the discovery of naturally occurring anti-microbial and anti-tumour alternatives. Certain flavonoids have a unique ring structure that can neutralize free radicals and thus reduce oxidative stress. The role of specific plant secondary metabolites for induction of apoptosis in target tissue has marked a milestone in oncological researches. This has also allowed scientists to synthesize drugs that mimic these plant secondary metabolites but with great target precision and less cytotoxic effect to the healthy cells. Plant-derived bioactive compounds seem promising alternatives to the synthetic anti-viral drugs for Covid-19. Some plant secondary metabolites inhibit essential proteins for viral replication thus inhibiting their propagation.

Conflict of Interest

None declared.

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None declared.

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