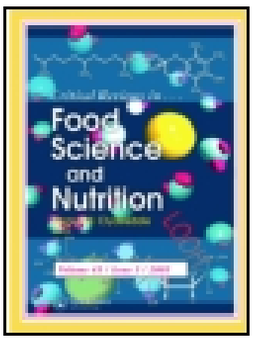

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REVIEW

Effects of phytochemicals on cellular signaling: reviewing their recent usage approaches

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ABSTRACT

Most of the previous studies in last three decades report evidence of interactions between the different phytochemicals and the proteins involved in signal transduction pathways using in silico, in vitro, ex vivo, and in vivo analyses. However, extrapolation of these findings for clinical purposes has not been that fruitful. The efficacy of the phytochemicals in vivo studies is limited by parameters such as solubility, metabolic degradation, excretion, etc. Various approaches have now been devised to circumvent these limitations. Recently, chemical modification of the phytochemicals are demonstrated to reduce some of the limitations and improve their efficacy. Similar to traditional medicines several combinatorial phytochemical formulations have shown to be more efficient. Further, phytochemicals have been reported to be even more efficient in the form of nanoparticles. However, systematic evaluation of their efficacy, mode of action in pathway modulation, usage and associated challenges is required to be done. The present review begins with basic understanding of how signaling cascades regulate cellular response and the consequences of their dysregulation further summarizing the developments and problems associated with the dietary phytochemicals and also discuss recent approaches in strengthening these compounds in pharmacological applications. Only context relevant studies have been reviewed. Considering the limitations and scope of the article, authors do not claim inclusion of all the early and recent studies.

KEYWORDS

Ex vivo; in silico; in vitro; in vivo; nanoparticles; phytochemicals

Introduction

Maintaining a sustainable health in the society has always remained a concern and the need has persuaded constant search for betterment in the quality of living and improvements in available therapies and strategies. Better conceptions on health, diseases and remedies have thus facilitated refinement and coarse corrections in the treatment approaches in coherence with scientific understanding. Emergence of biomedicine, scientific acceptability of traditional medicine and understanding on the implications of nutrition has uplifted the outlook toward health and diseases. Although this provided vital understanding on the pathogenesis and treatment of certain ailments, several life threatening diseases still remain a challenge. Based on an investigation from 1990 to 2010, the leading cause of early death and disability in the United States is due to diet (Murray et al. 2013). According to the World Health Organization (WHO) report, Cardiovascular diseases (CVDs) are the major cause of death and according to global estimates 17.9 million people died from CVDs in 2016 (https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)). Cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018 (https://www.who.int/news-room/fact-sheets/detail/cancer). Interestingly in the past few decades, dietary supplement from plants has been considered to be effective in preventing and/or in treating various diseases (Cardozo et al. 2013).

In this context, increased consumption of vegetables and fruits (He, Nowson, and MacGregor 2006; Lai and Roy 2004) has been shown to be associated with a reduced risk of many fatal diseases, like cancer (Riboli and Norat 2003), cardiovascular disease (Khalesi, Irwin, and Schubert 2015; Medina-Remon et al. 2015), neurodegenerative diseases (Commenges et al. 2000) and hyperinsulinemia (Bahadoran et al. 2015). This association might be due to the presence of various phytonutrients that are naturally present in plant-based foods (Gupta et al. 2010; Liu 2003; Rescigno, Tecce, and Capasso 2018). Bioactive phytochemicals are abundant in fruits, tea, vegetables and whole grains, etc. (Probst, Guan, and Kent 2017). These Phytochemicals, that classified

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into several categories based on its structure or function (e.g., phenolic acids, thiols, carotenoids, ascorbic acid, tocopherols, sulforaphane, indoles, isothiocyanates and glucosinolates) (Bohn 2014; Yang and Xiao 2013), interact with more than one molecular target, thereby alter diverse signaling pathways (Liu 2003). While there is an ever growing amount of literature available on the molecular mechanism involved in the function of phytochemicals, it is imminent to document the signaling mechanisms that are possibly influenced by bio-active phytochemicals. With this objective, this review summarizes the beneficial roles and limitations associated with the dietary phytochemicals and also discusses on the recent approaches to strengthen the functions of these compounds for their pharmacological applications.

A variety of micro-environmental cues are integrated by signal transduction pathways to guide the cell function by regulating cell cycle status, gene transcription, cell growth and differentiation (Schade et al. 2006). Since past few decades, it is widely understood that defects and alteration in signaling pathways are the major underlying cause of diseases (Schade et al. 2006). Recent experimental studies have reported alterations in signal transduction pathways tumor development, progression and immune evasion (Nicolini et al. 2018), most aging associated diseases are also due to alterations in signal transduction pathways (Berridge 2014). It has been recently reported that age related changes in TGF-β signaling and in protein kinase and phosphoprotein phosphatase activities in chondrocytes with advancing age lead to inflammation and osteoarthritis (Berridge 2014). Mutations or defects in growth factors, hormones, or other stimulating molecules are the main causes of dysfunction of cellular signaling (Scott and Pawson 2000). All differentiated cells have their specific signaling complex called signalosome which functions to generate normal output signals used by every cell for controlling its specific function (Berridge 2012). The framework for considering signal transduction related defects to the occurrence of diseases can be understood in terms of these signalosome complexes. It is noteworthy that the complexity of signaling system poses a huge challenge to research and as per current understanding, use of chemical compounds (phytochemicals/natural compounds) may serve as activators or inhibitors of these signaling mechanisms and the phenotypic alteration can be controlled to prevent/treatment of disease by developing novel therapeutic targets. Table 1 lists out the types of some popular examples of phytochemicals and some of their therapeutic actions.

Various types of phytochemicals and their therapeutic potential

Polyphenols

Polyphenols are a class of naturally occurring compounds present essentially in vegetables, fruits, cereals and beverages (Scalbert et al. 2005; Spencer et al. 2008) and they represent ubiquitous phenolic compounds that occur as secondary metabolites in the plant kingdom (Figueira et al. 2017). During recent decades, epidemiological studies have highlighted the beneficial effects offered by consumption of polyphenols rich diet toward development of cardiovascular disorders, cancers, diabetes and other neurodegenerative diseases (Graf et al. 2010). Around more than 8,000 polyphenolic compounds have been identified from a variety of plant species (Arts and Hollman 2005) while a recent review done by Pimentel-Moral et al. (2018) reported occurrence of at least 10,000 unique polyphenols (Pimentel-Moral et al. 2018). All phenolic compounds of plants arise from a common intermediate, phenylalanine or a close precursor shikimic acid (Lin et al. 2016). Majorly, they exist in conjugated forms with one or more sugar residues linked to hydroxyl groups, although linkages to the sugar (polysaccharides/monosaccharide's) to an aromatic carbon (in compounds like carboxylic and organic acids, lipids, amines, and linkages with other phenol) also exist (Kondratyuk and Pezzuto 2004). On the basis of number of phenol rings present and the structural elements that bind these rings to one another, polyphenols can be classified into different groups. The different classes of polyphenols include- Flavonoids, Anthoxanthins, Flavanones, Flavones, Isoflavones, Phenolic acids, Hydroxybenzoic acids, Trihydroxy stilbenes, Tannins and Diferuloylmethane (Scalbert et al. 2005). Considering the therapeutic applications of polyphenols, there are innumerable instances of their health benefits. In fact, it is also reported that polyphenolic rich foods and beverages enhance the antioxidant capacity which is often linked to their biological activity. In polyphenols, the phenolic groups accept an electron to form relatively stable phenoxyl radicals, thereby disrupting chain oxidation reactions in cellular components. The rise in antioxidant effect of plasma is attributed to the presence of reducing polyphenols and metabolites in plasma, which further effects the concentrations of other endogenous reducing agents in plasma or by effecting the absorption of pro-oxidative agents such as iron (Scalbert et al. 2005). The protective effect of polyphenols has also been indicated in preventing oxidative damage to lymphocytic DNA (Xavier et al. 2002). These protective properties of polyphenolics are also used up in limiting the risk of various degenerative diseases associated with oxidative stress (Luqman and Rizvi 2006; Pandey, Mishra, and Rizvi 2009; Pandey and Rizvi 2010).

Dietary flavonoids

Flavonoids constitute the most widely studied group of polyphenols. Flovanoids comprise of a common basic structure having two aromatic rings bound together by three carbon atoms forming an oxygenated heterocycle (de Groot and Rauen 1998). Till date around 4,000 varieties of flavonoids have been identified, most of them are responsible for the attractive colors to fruits, flowers and leaves. On the basis of type of heterocycle involved, flavonoids may further be classified into six subclasses: flavanols, flavanones, isoflavones, flavan-3-ols, flavones and anthocyanins. Individual differences within each group lie in arrangement and number of hydroxyl groups and extent of their alkylation and/or glycosylation. For example Quercetin, catechins and

Table 1. Phytochemicals and some of their therapeutic actions.

S. No.	Phytochemical	Class/type	Therapeutic effects	
1	Morphine	Alkaloid	Analgesic	Acts as a strong agonist of μ opioid receptor (MOR) (Lipp 1991; Hashimoto et al. 2006), inhibit nociceptive stimuli (Wang et al. 2009)
2	Codeine	Alkaloid	a) Analgesic b) Antidiarrheal	strong agonist of μ opioid receptor (Bradley and Nicholson 1986), Increase net intestinal absorption (Schiller et al. 1982)
3	Nicotine	Alkaloid	a) Stimulant b) Neuro-protection	Activates nAChRs and increases the release of neurotransmitters (Pontieri et al. 1996) Anti-inflammatory effects via activation of α7 nicotinic receptors in microglial cells (De Simone et al. 2005)
4	Reserpine	Alkaloid	Anti-hypertensive (Shamon and Perez 2016)	acting on the vasomotor center of brain, it leads to generalized vasodilatation (Mc, Doyle, and Smirk 1954)
5	Vinblastin	Alkaloid	Anti-cancer	Mitotic arrest by inhibiting tubulin polymerization and mitotic spindle formation (Thirumaran, Prendergast, and Gilman 2007; Toso et al. 1993; Wendell, Wilson, and Jordan 1993)
6	Caffeine	Alkaloid	a) Central nervous system Stimulant b) Neuroprotection	Block A1 receptor-mediated inhibition of mesopontine cholinergic projection neurons involved in the regulation of cortical activity (Rainnie et al. 1994) Blockade of A2A receptors (Chen et al. 2001)
7	Colchicine	Alkaloid	Used to treat gout	Tubulin Disruption to affect the viability of cells involved in gout associated inflammation (Andreu and Timasheff 1982; Ning et al. 2014); Interrupts NLRP3 inflammasomeactivation (Martinon et al. 2006); Inhibition of Superoxide Anion Production (Chia, Grainger, and Harper 2009); boosts antioxidant redox system (Şahin et al. 2011)
8	Ajmaline	Alkaloid	Anti-arrhythmic	Sodium channel blocker (Brugada et al. 2000)
9	Emetine	Alkaloid	a) Anti-protozoal drug b) Therapy for pulmonary arterial hypertension c) Anti-viral	Inhibits protein biosynthesis and acts as DNA intercalator (Krstin et al. 2016) Inhibits pulmonary artery smooth muscle cells proliferation with anti-inflammatory effects, leading to the recovery of mitochondrial function (Siddique et al. 2019) Inhibits viral replication and decreases viral entry (Yang et al. 2018; Khandelwal et al. 2017)
10	Quinine	Alkaloid	Anti-malaria drug	Blocks of heme crystal growth (Sullivan 2017)
11	Quercetin	Flavonoid (Polyphenol)	a) Anti-artherosclerosis b) Anti-cancer (Matsukawa et al. 1997) c) Anti-neurodegenerative d) Anti-allergic e) Anti-hypertensive	Regulates the expression of PCSK9, CD36, PPARγ, LXRα and ABCA1(Jia et al. 2019) Cell cycle arrest, activates ChK2 to regulate p21 expression, downregulates cyclinB1 and CDK1, inhibits NF-κB-evoked pathways, inhibits TNF-α (Kedhari Sundaram et al. 2019; Vidya Priyadarsini et al. 2010) activates PKD1-Akt cell survival signaling (Ay et al. 2017) Suppresses neuropeptide production, relaxes airway smooth muscles (Townsend and Emala 2013; Kashiwabara et al. 2016), balances Th-1 and Th-2 levels (Nair et al. 2002), Inhibits mast cell activation (Johri et al. 1985), reduces TNF-α, IL-1β, IL-6, and IL-8(Min et al. 2007) Ameliorates pulmonary hypertension by reducing 5-HT_{2A} receptor expression and Akt and S6 phosphorylation and by partially restoringKv currents (Morales-Cano et al. 2014), Attenuates hypertension associated cardiac effects by enhancing PPAR- γ and suppressing AP-1 activity (Yan et al. 2013)
12	Catechin	Flavonoid (Polyphenol)	Anti-oxidant, vasodilation	Free radical scavenging (Wang et al. 2017), Ca(2+) antagonist (Ghayur, Khan, and Gilani 2007)
15	Anthocyanins	Flavonoid (Polyphenol)	Hypoglycemic, neuro-protective	Protects β-cell proliferation (Hong et al. 2013) Suppresses neuro-inflammation (Pan et al. 2018)
17	Resveratrol	Stilbene (Polyphenol)	a) Anti-diabetic b) Anti-cancer c) Cardio-protective	Shows antioxidant activities and improves islet function, promotes muscle glucose uptake and inhibites the expression of p-ERK (Li et al. 2018) Improve oxidative capacities of cancer cells through CamKKB/AMPK pathway (Saunier et al. 2017) Induces mitochondrial respiration and apoptosis (Blanquer-Rossello et al. 2017) Regulates autophagy by enhancing SIRT1/FOXO1/Rab7 aginats diabetic cardiomyopathy (Wang et al. 2014)
18	Inulin	Polysaccharide	a) Anti-hyperglycemic b) Anti-hypercholesterolemia	Restores Leptin-related Pathways (Song et al. 2019), improves insulin sensitivity (Chambers et al. 2019) Alters hepatic lipid metabolism, Increases browning markers such as Pgc1α, Ucp1, Cidea (Weitkunat et al. 2017)

myricetin are some of the commonest examples of known (Spencer et al. 2008). In plant tissues, flavonoids are stored as various derivatives, commonly as sugar O-conjugates. The commonly bound sugars are mostly glucose, xylose, galactose, rutinose, arabinopyranose, arabinofuranose and rhamnose. Such modification determines the bioavailability and absorption of flavonoids. On ingestion, the sugar moieties in the phenolic backbone of flavonoids such as quercetin are cleaved and majorly absorbed in the small intestine although a minor portion is absorbed in the gastrium. Glycosylated flavonoids are hydrolyzed by the action of lactase phlorizin hydrolase or β-glucosidase the flavonoids are hydrolyzed and the aglycones are subsequently taken-up by epithelial cell (Day et al. 2000; Marin et al. 2015). And those glycosylates resistant to lactase phlorizin hydrolase or β-glucosidase are not absorbed by small intestine. Flavonoids with rhamnose moiety reach colon to be hydrolyzed by the gut enzyme α-rhamnosidases for absorption. Non-glycosylated flavonoids such as (−)-epicatechins are absorbed without hydrolysis. High molecular weight flavonoids such as proanthocyanidins are as such not likely to be absorbed in the small intestine. Flavonol glucosides in onion fries are detectable as

hydrolyzed forms in the circulatory system within 30 min of ingestion. The time taken to reach peak plasma concentrations (T_{max}) of hydrolyzed flavonoids were less than 1 h and metabolites were quickly removed from the bloodstream with their short elimination half-life ($T_{1/2}$). Pharmacokinetic analysis of different metabolites detected from blood after consumption of various sources of polyphenols will benefit in determining required intake amounts for therapeutic outcomes.

Flavonoids have gained much popularity as very efficient brain disorder preventatives due to their potent anti-oxidant properties (Elumalai and Lakshmi 2016). For example, quercetin is very apt in reducing cancer, allergies, neurodegenerative diseases, cardio-vascular diseases hypertension etc., due to its very high anti-oxidant and anti-inflammatory properties (Elumalai and Lakshmi 2016). Polyphenols found in green tea have been reported in many relevant studies to be potent anti-oxidants that play important role in regulation of signaling pathways like NF$\kappa\beta$ mediated IκB kinase complex pathways, programed cell death pathways and interventions involving surge of inflammatory markers such as COX-2, cytokines etc (Oz 2017). Among various varieties of polyphenols, phenolic acids, are directly associated to response against stress, in healing process for lignification of damaged areas, possess antimicrobial properties and concentrations may increase after pathogenic infections (Parr and Paul Bolwell 2000). A class of polyphenols called stilbenes, contains two phenyl moieties linked by a two- carbon methylene bridge. Although, their occurrence in humans is low but most stilbenes in plants act as antifungal phytoalexins. One of the widely occurring and best studied is resveratrol (3,4′,5-trihydroxystilbene) found largely in grapes and their product red wine (Riviere, Pawlus, and Merillon 2012; Pandey and Rizvi 2009). Resveratrol is found in peanuts; grapes etc. and are effective against diseases like diabetes and cancer. Resveratrol exhibits cardio-protection as proved by superior post-ischemic ventricular recovery, decrease in number of apoptotic cardiomyocytes, decreased myocardial infarct size upon treatment in appropriate animal models (Kamaleddin 2016). In this way and with many other experimental evidences, it is quite obvious that polyphenols are highly potent therapeutic agents however, there are certain limitations with their therapeutic potency like low bioavailability, side effects etc.

Dietary alkaloids

While plant sources of alkaloids remain an important part of normal modern diet, it has been used since ancient times as narcotics, poisons, insecticides and medicines. Alkaloids have continued to be the object of human interest owing to their safe utilization and several health benefits. Alkaloids are commonly found in families of flowering plants with more than 4,000 species identified. The first alkaloid to be isolated and crystallized was active constituent of opium poppy (Hoolihan 1994). Generally a given species contains only few kinds of alkaloids but both opium poppy and ergo- contains about 30 different types. Certain plant families are highly rich in alkaloids such as *Papaveraceae*, *Ranunculaceae*, *Solanaceae*. The presence of alkaloids is abundant in higher plants as at least 25% of higher plants contain these molecules. Arguments are put forth to elucidate dietary alkaloids as to inflict minimal influence on biological receptors and activity as they are generally present as trace amounts (less than 10 gms per kg plant mass) (Montagne 1997). Interest in alkaloids rises due to their wide medicinal importance. For example, harmane-β-carboline alkaloid widely found in maize, barley, soy, vegetable, fruit, juices coffee and in products of plant origin such as bread, cookies, coffee substitutes (such as chicory coffee) and in fermented alcoholic beverages (Herraiz 2004; Herraiz 2002; Alves et al. 2010; Casal 2015; Piechowska, Zawirska-Wojtasiak, and Mildner-Szkudlarz 2019). Harmane-β-carboline show many pharmacological activities like anti-depressant, anti-anxiety, anti-diabetic, anti-parasitic, anti-oxidant etc. However, it also exhibits tremorogenic activity along with adverse effects on learning and memory (Khan, Patel, and Kamal 2017). Morphine is used as powerful narcotic, for pain relief but its use is limited due to addictive properties. Morphine is a powerful narcotic; a recent study has however reported effective control of post-operative pain by addition of bupivacaine to morphine with lesser side effects (Mercadante 2013). Codeine, the methyl ether derivative of morphine is found to be better in terms of least addictive action for pain relief. Codeine is a pro-drug having little pharmacological activity and needs to be metabolized in the liver to form morphine that produces codeine's analgesic effects (Idema 2011). Since many decades, codeine has been prescribed to pediatric patients as an analgesic and antitussive compound but individual patient response toward codeine varies significantly as there is substantial genetic variation in the activity of CYP2D6 (liver enzyme) that metabolizes codeine (D Tobias et al. 2016; Sanel et al. 2016). Rotenone being a mitochondrial complex-1 inhibitor has been shown to induce up-regulation of glaucoma related proteins like myocilin, MMP9, IL-6 in the in vitro culture of human trabecular meshwork, indicating that a prolonged exposure to it even in low doses can adversely affect human trabecular meshwork through senescence and consequent apoptosis (Maurya, Agarwal, and Ghosh 2016).

Berberine (*Berberis vulgaris*), an isoquinoline alkaloid has anti-viral, anti-diarrhea, anti-microbial, anti-tumor and anti-inflammatory effects (Mirhadi, Rezaee, and Malaekeh-Nikouei 2018). Not only this, it is effective against type 2 diabetes, congestive heart failure, hypertension, cardiac arrhythmia and improves lipid and glucose metabolism (Mirhadi, Rezaee, and Malaekeh-Nikouei 2018). Caffeine, a xanthine alkaloid, is a nervous stimulant drug that affects the functioning of the cardiovascular, respiratory, renal, and nervous systems gets metabolized in the liver into three primary metabolites: paraxanthine (84%), theobromine (12%), and theophylline (4%). Paraxanthine: Has the effect of increasing lipolysis, leading to elevated glycerol and free fatty acid levels in the blood plasma. Theobromine: Dilates blood vessels and increases urine volume. Theobromine is

also the principal alkaloid in cocoa, and therefore chocolate. Theophylline: Relaxes smooth muscles of the bronchi, and is used to treat asthma. The therapeutic dose of theophylline, however, is many times greater than the levels attained from caffeine metabolism (Hoensch and Oertel 2001).

Polysaccharides

Polysaccharides are complex carbohydrates which are composed of 10–1000, monosaccharide units arranged in chains. Polysaccharides derived from plant sources are known to possess bioactive properties. Bioactive polysaccharides derived from plants are comprised of dietary Fibers, herbs and wood plants (Harhaji Trajkovic et al. 2009; Liu, Willför, and Xu 2015). As per the definition of Food and Agriculture Organization, bioactive polysaccharides are a variety of indigestible plant polysaccharides including celluloses, hemicelluloses, oligosaccharides, pectin and several other lignified compounds. In natural form, they are quite helpful in maintaining good health. For instance, cellulose can instantly stimulate the bowel movement and inulin needs to be fermented into short- chain fatty-acids by microflora so as to prevent numerous gastrointestinal disorders (Pool-Zobel 2005). Further, polysaccharides such as inulin, pectins and gums are also known to play crucial role in disease prevention by their ability to retard the movement of food in digestive tract, reduce blood cholesterol levels, and avoiding sudden hyperglycemia after food intake (Chawla and Patil 2010; Tungland and Meyer 2002). A recent development is the work done by Singla et al. (2017) have speculated that nanocomposites of plant cellulose nanocrystals formed by binding bovine serum albumin and human serum albumin possess more cholesterol effluxing ability and hence these may be considered potential candidate for use in pharmaceuticals (Singla et al. 2017). There are increasing evidences convincing that moderate or higher intake of dietary fibers effectively reduces the risk for developing cardiovascular diseases such as stroke (Casiglia et al. 2013). In countries like China, Japan and in India even polysaccharides derived from herbs are found to form an integral component of traditional medicines (such as Japanese Kampo medicines, traditional Chinese medicines and Indian Ayurveda system) for treatment of ailments and illnesses (Tang, Hemm, and Bertram 2003a, 2003b). For instance, *Ganoderma lucidum* polysaccharides that are used in traditional Chinese medicine for cancer prevention (Na et al. 2017). Triphla herbal extract is potent anti-inflammatory substance that can be used in treatment of arthritis as it has been found to suppress inflammatory mediators like TNF-α, MCP-1, NO, VEGF etc., intracellular free radicals and lysosomal enzymes like acid phosphatase, cathepsin D etc. in lipopolysaccharide stimulated-RAW 264.7 macrophages (Kalaiselvan and Rasool 2016). Indeed, for herbal medicines, polysaccharides have been discovered as the active ingredient responsible for several pharmacological activities such as immuno-stimulatory activity, antioxidant, antiviral activity, anti-tumor activity and protective roles in radioprotection effect, hepatoprotection and anti-fatigue effect (Thakur et al. 2012; Li and Peng 2013; Harlev et al. 2012). Starch based hydrogel formulations like that developed from *Dioscorea hispida* are eco-friendly and non-cytotoxic and are promising smart materials to have many biomedical and pharmaceutical applications (Ashri et al. 2018). Polysaccharides derived from herbs are active in their native form to stimulate human immune systems, to inhibit lipid peroxidation and scavenge free radicals. Polysaccharides like xylans from softwood, hardwood also possess immense prebiotic potential for use in both nutrition and medical research (Holtzapple 2003). Polysaccharides have been increasingly utilized in developing effective drug delivery systems, for instance, that developed by Singh and Kumar (2018), where they used moringa gum in formation of a hydrogel that can be used in delivering antibiotics slowly and effectively in the GIT (Singh and Kumar 2018).

Essential oils

Essential oils (EO) are another major type of secondary metabolites obtained from plant extracts with antimicrobial properties. These are volatile, hydrophobic, complex compounds having strong odor. An EO is a naturally occurring volatile component responsible for imparting characteristic color and essence to its source plants and spices. Contrary to their name, EO are not true oils (i.e., lipids) but are derived from component responsible for fragrance or *Quinta essentia* of plants. EO are considered safe for human and animal consumption and are Generally Recognized As safe (GRAS; FDA 2004) in USA. As far as occurrence is considered EO mainly found in edible, herbal and medicinal plants. Since these aromatic compounds are highly volatile therefore they are extracted by steam distillation or solvent extraction methods. EO can be extracted from different parts of the plant including flowers, stem leaves, roots, seeds and barks (Greathead 2003). Of note, the composition may also vary from different parts of same plant. Chemical differences among EO obtained from individual plants or different varieties of plants also exist and are attributed to age of plant, genetic composition and environmental factors (Cosentino et al. 1999). Along with diterpenes and low-molecular weight aliphatic hydrocarbons, alcohols, acids, aldehydes, esters and N and S containing compounds may also be present (Dorman and Deans 2000). Talking about the therapeutic applications of EOs, many studies suggest them to be very effective in variety of conditions ranging from mild to severe ones. Many EOs exhibit the antimicrobial properties against a variety of microorganisms ranging from bacteria, fungi, and protozoa and food-borne pathogens such as *Escherichia coli* (Chao, Young, and Oberg 2000; Sivropoulou et al. 1996; Deans and Ritchie 1987). Many recent studies have also found EOs to be effective against many pathogenic bacteria. The EO from *Alpinia zerumbet* is suggested to be useful for clinical management of secondary effects cerebral vascular disease (Maia et al. 2016). Another study shows that bio-adhesive gels containing EOs promote wound healing and prevent post-operative infection and pain (Scotti et al. 2018). In addition to immunotherapy for

allergic rhinitis many natural products have been found to be useful alternatives with few such examples being cinnamon bark, cellulose powder, Spanish needle, capsaicin and also the EO of *Nigella sativa* seeds (Ipci et al. 2016). The EO of *Nigella sativa* seeds is reported to have anti-histaminic properties and inhibits cyclooxygenase and 5-lipoxygenase signaling pathways of arachidonic acid metabolism thus acting as anti-inflammatory compound (Ipci et al. 2016). All these and many more studies have confirmed the therapeutic utility of EOs from a variety of plants.

Phytochemicals that influence various signaling pathways

In silico studies

Molecular docking is a powerful tool to obtain insight about the most probable binding conformation of phytochemicals, required to explain the reasons for their potency. Since, the evidences obtained from in silico analysis are based on predictions, further in vitro or animal or clinical studies are essential to confirm the results. With caution, in silico analysis shall not only be used to narrow down vast quantity of resources but also to predict solutions for complication associated with the structural properties of a phytochemical that are strongly associated with their activity. Bromelain, an inflammatory drug is an efficient anti-inflammatory agent however their usage is limited due to their instability at high temperatures. However, phytochemical complexes formed with bromelain may enhance their stability. In a recent report by Mohamed et al. (2018) the natural compounds isolated from Malaysian herbs that were able to show strong bonding with bromelain were investigated for their effect on the activity of enzyme Phospholipase A2 (P1a2), which induces inflammatory response. The study investigated the potential of bromelain-phytochemical complex inhibitors using a combination of in silico docking studies that used a bromelain model prepared by Autodock tool and the results were corroborated with in vitro methods as well. Three compounds from dietary and herbal sources-a saponin-asiaticoside, a biflavonoid-amentoflavone and a sapogenin-diosgenin gained attention for further experimental work. The outcome of these investigations showed that Bromelain-amenthoflavone exerts antagonistic effects on PIA2 whereas complex of Bromelian-asiaticoside and Bromelain-diosgenin showed synergistic effects at high concentrations of combined compounds and antagonistic effects at low concentrations. Such data provide significant implications for use of bromelain with asiaticoside and diosgenin in treating inflammation (Mohamed et al. 2018). In several other reports, dietary phytochemicals have also been investigated for their anti-inflammatory and anti-tumor properties. These properties were validated by using docking protocols and explicate the possible mechanism of action for a dataset of nine phytochemicals namely emodin, ellagic acid, boswellic acid, 1-caffeoylquinic acid, genistein, guggulsterone, quercetin, resveratrol and sylibinin against the nuclear factor-kappaB (NF-kβ) precursor protein p105, a transcription factor overexpressed in breast cancer (Khan et al. 2013). 2-Dimensional structures of the nine phytochemicals were converted into 3-D structures using an online software system CORINA and the X-ray crystallographic structure of NF-κB precursor p105 was obtained from Brookhaven Protein Data Bank (Docking studies were carried out using AutoDock Tools 4.0). A significant binding affinity could be observed with different phytochemicals with the Rel homology domain of NF-kβ precursor protein p105. 1-caffeoylquinic acid and quercetin were found to be very effective against target molecule with a binding energy of -11.50 kcal/mol and -12.11 kcal/mol, respectively.

It is widely known that Phosphatase and Tensin homolog located on chromosome 10q23 is inactivated in a subset and AKT is activated in cancer. The PTEN is the central negative regulator of phosphatidylinositol 3-kinase (PI3K/AKT) signaling cascade. The anti-cancer potency of thymoquinone (TQ) was investigated by analyzing the interaction between TQ with the target protein PTEN and suggested that TQ might inhibit abnormal cell proliferation occurring in cancer by changing the activity of PTEN (Nithya, Ilakkia, and Sakthisekaran 2015). The three dimensional structure of TQ was obtained using in silico methods, and the structure of PTEN is obtained from NCBI-protein data bank and 3D structure was predicted by using m align and model-default operations of the modeling tool Modeller9v1. The active site on PTEN was predicted by Q-site finder and a 403 residue in PTEN was identified as the target domain. TQ was docked to the active site on PTEN using AutoDock Tools 4.0 and TQ was confirmed to strongly target PTEN.

In silico studies have been done to identify novel potent inhibitors against parasitic diseases. For instance, using homology modeling, 3D models of MAPKs (LmxMPK4, PfMAP2 and TBMAP5) from three parasites *Leishmania mexicana*, *Plasmodium falciparum*, and *Trypanosoma brucei* were developed and ten phytoligands were used for molecular docking (Gupta et al. 2016). 3D structure of LmxMPK4 was obtained by Homology modeling using MODELER tool which generated many preliminary models that were ranked based on their DOPE (Discrete Optimized Potential Energy) scores. Models with the low DOPE score were chosen to verify the stereo chemical properties of target protein structure. Out of these ten phytoligands, two namely, aspidocarpine (for LmxMPK4 and TBMAP5) and cubebin (for PfMAP2) were found to be effective inhibitors that exhibited inhibitory effects comparable to those of control drugs and thus, these are strong candidates for treating these parasitic infestations (Gupta et al. 2016). Another significant docking based study shows that *Salvia sclarea* (clary sage; clary), used as a spice, has effective activity against the enzymes (like tyrosinase, α-glucosidase, α-amylase, acetylcholinesterase etc.) involved in pathogenesis of many common human ailments (Zengin et al. 2018). Bioactive substances such as protocatecheuic acid, catechin, phydroxybenzoicacid, caffeic acid, o-coumaric acid (2-hydroxycinnamic acid), rutin, rosmarinicacid, luteolin and apigenin from *S. sclarea* extract, were chosen and the 3D structure was obtained from Zinc database. The results show that most bioactive compounds in *S. sclarea* extract efficiently

target α-glucosidase and thereby can alleviate diabetes associated complications.

A recent ethnomedicine claim directed in silico study has indicated promising anti-tumor activity by traditionally utilized medicinal plants and phytochemicals like alkaloids, terpenoids, glycosides, phenolics etc. (Girma et al. 2018). About 18 medicinal plants identified and their phytochemicals were listed based on available literature phytochemicals were subjected to in silico evaluation on their anti-cancer activity using a web server named Cancer Drug (CDRUG; http://bsb.kiz.ac.cn/CDRUG/). 34 compounds were predicted to have anticancer activity and terpenes (17) were seen to be the common anticancer drug among them.

In yet another recent in silico study that has predicted specific plant secondary metabolites like coptisine, chrysothrone, annoretine, thalicminine etc. to be genotoxic and carcinogenic (Gluck et al. 2018). Molecular docking and dynamics simulation studies have been done in addition to determination of IC_{50} to demonstrate that acylphenols obtained from *Myristica fatua Houtt*. Apart from the above mentioned studies there are many others conducted in recent past that indicate a wide variety of therapeutic applications of phytochemicals like activity of Gingerenone-A and Shogaol (source ginger) against antibiotic resistant *Staphylococcus aureus* (Rampogu et al. 2018) anti-virulence drug activity against *Pseudomonas aeruginosa* (Musthafa et al. 2017) multi-target inhibitory activity for inflammatory pathways (Devi et al. 2017) to mention a few.

In vitro studies

Since a very long time during the 20th century many in vitro studies have been done world-wide to assess the effects of phytochemicals on different types of cells. Numerous polyphenolic flavonoids have been proven to display strong anti-inflammatory properties and has invoked interest in developing safe and effective treatment strategies against oxidative stress related cellular disorders. Study conducted by Bak et al. showed that 35 µg/mL of wild grape seed procyanidins in RAW 264.7 murine macrophages retard the production of oxidative stress mediators (such as ROS and NO by preventing the activation of NF-kB and p38 mitogen-activated protein (Bak et al. 2013). Phytochemicals derived from Brassica such as sulforaphane (SFN), phenethyl-isothiocyanate (PEITC) and indole-3-carbinol (I3C) are also known to exert anti-inflammatory effect by downregulation of LPS induced expression of NO, COX-2, iNOS by inhibiting NF-kB pathways in mouse macrophages. SFN (50 µM) reduced the NO levels in LPS (500 ng/ml) treated Raw 264.7 murine macrophages by 25%. The anti-inflammatory effect of SFN was mediated by transactivation of κB-dependent genes and by inhibiting DNA binding activity of NF-κB possibly by modulating the intracellular redox conditions through dithiocarbamoylation of thiol groups essential for NF-κB activation (Heiss et al. 2001). In a study reported by Tsai et al on LPS (330 ng/mL) stimulated macrophages, 50 µM of I3C and 5 µM of PEITC was found to effectively reduce the levels of NO production. The study conclude that I3C potentially acts by reducing the expression of iNOS, interfering with the activity of iNOS enzyme, and by directly binding and trapping NO to reduce NO availability, and PEITC largely acts by reducing the expression of iNOS and by direct interaction with NO (Tsai, Liu, and Chen 2010).

Earlier investigations suggest that phenolic compounds (Glycoside oleuropein, hydroxytyrosol, and tyrosol) from extra-virgin olive oil (EVOO) exhibit effective anti-inflammatory activity by blocking eicosanoids (Storniolo et al. 2019; Santangelo et al. 2007; Storniolo and Moreno 2016; Cardeno et al. 2014). In case of LPS stimulated macrophages, the phenolic component of EVOO such as hydroxytyrosol (200 µM) was able inhibit macrophage activation by suppressing the transcriptional levels of iNOS and COX-2; The results were also correlated with hydroxytyrosol mediated reduction in LPS-induced ROS generation also correlated with inhibition of NF-κB, STAT-1αand IRF-1 protein levels (Maiuri et al. 2005). Further, EVOO (10 g) has been reported to elicit protection against post-prandial oxidative stress by downregulating NOX2. (Carnevale et al. 2014).Tea, the second most commonly consumed beverage of the world is a rich source of polyphenols and it has been shown that these have chemo-protective effect against UV-B induced skin cancer due to their significant role in DNA repair, signaling pathways, inflammation and oxidative stress etc. The action of tea polyphenolics primarily epicatechin-3-gallate (EGCG), and epigallocatechin (EGC) has been described as chemo-preventive as they induce anti-inflammatory effect in cancer cells by reducing the LPS induced TNF-α generation and preventing the activation of NF-kβ (Johnson, Bailey, and Mukhtar 2010; Stangl et al. 2007; Lin et al. 1999). In Hodgkin's lymphoma cell lines 25 µM of EGC treatment inhibited the binding of NF-kβ to DNA by 40–42% in a mechanism independent of their antioxidant effect (Mackenzie and Oteiza 2006). EGCG (10–80 µM) reduces the cytoplasmic and nuclear levels of NF-kβ in a dose-dependent manner in human epidermoid carcinoma (A431) cells and normal human epidermal keratinocytes (NHEK), although at different concentrations (Ahmad, Gupta, and Mukhtar 2000). EGCG (20–50 µg/mL) treated on human THP-1 cells cultured with of LPS 500 ng/mL/anti-β2GPI (10 µg/mL)/β2GPI (100 µg/mL) complex showed reduction in the expression of tissue factor and TNF-α by blocking the TLRs-MAPKs- NF-kβ signaling axis (Wang et al. 2014). Black tea has also been reported in vitro and pre-clinically to have many bioactive compounds like alkaloids, polyphenols, amino acids etc. that make it regulate many molecular targets such as COX-2, MAPK, AP-1, 5-LOX, JNK, STAT, Bcl2, AKT, caspases, p53 etc. and thus prevent and even cure cancer (Singh et al. 2017). Kaempferol, a flavanoid widely distributed in dietary sources, such as tea, broccoli, apples, strawberries, and beans, also reduces inflammation by inhibiting the generation of PGE2. Various evidences have revealed the anti-inflammatory mechanism of cocoa polyphenolics such as inhibition of mitogen induced activation of T cells and inhibited expression of IL-2 and other cytokines (Chen and Chen 2013). Zhuang et al. showed that kaempferol (25–100 µM) reverses

the stimulation of interleukin-1β by inhibiting NF-κB pathway in Rat Osteoarthritis Chondrocytes thereby determined anti-inflammatory and anti-arthritis effects of kaempferol (Zhuang, Ye, and Huang 2017). Curcumin has been shown to have anti-inflammatory and anti-oxidant effects in vitro upon application in cultured astrocytes and inhibit MAPK pathway and thus expected to be useful against temporal lobe epilepsy (Drion et al. 2018).

Chemoprevention is one of the promising therapeutic properties displayed by numerous dietary phytochemicals. Pterostilbene an active stilbene nanoflavanoid found in almonds (Xie and Bolling 2014), blueberries (Roupe et al. 2006), with low toxicity and 10 times higher bioavailability than resveratrol exhibits (Chatterjee et al. 2019; Peng et al. 2018), hallmark characteristics of an anti-cancer agent as it elicits anti-proliferative (5–100 µM) (Wawszczyk et al. 2014) and cytotoxic effects (40–100 µM) (Wawszczyk et al. 2014) on human colon cancer Caco-2 cells (IC_{50}75 µM) (Nutakul et al. 2011) in a dose and time dependent manner. The in vitro anti-proliferative and apoptotic effects of pterostilbene (25–75 µM) were also observed in breast cancer cells which were mediated through activation and overexpression of Bax which resulted in the increase of MnSOD in MDA-MB-231 cells (Moon et al. 2013). There are several in vitro studies confirming these effects of phytochemicals in breast carcinoma cell lines. Quercetin (50 µM) affects MCF-7cells by apoptosis and necroptosis mediated through multiple cell death pathways. Apoptosis was associated with increase in the levels of Bax and Caspase-3 and decrease in the levels of Bcl-2. Meanwhile necroptosis was associated with receptor interacting protein kinase (RIPK)-1 and RIPK-3(Khorsandi et al. 2017). Dietary carotenoidlutein (0.5–2 µM) inhibited various breast cancer cell lines including MCF-7 [ER/PR + HER2−], MDA-MB-468 [triple-negative], BT-474 (ER/PR + HER2+), MDA-MB-453 (triple-negative), and MDA-MB-231(triple-negative) by elevation in ROS generation, increasing the levels of chaperonin HSP60 and by p53 activation (Gong et al. 2018).Treatment of breast cancer cell lines with cocktail of six phytochemicals (indole-3-carbinol, resveratrol, genistein and curcumin, C-phycocyanin, quercetin), which were not effective individually, caused a marked suppression in proliferation by more than 80% and inhibited cellular motility by downregulation of proliferating cell nuclear antigen (PCNA), Retinoblastoma protein, Survivin, Cyclin dependent kinases4, BcL-2 and CD44 expression (Ouhtit et al. 2013).

Phytochemicals such as phytosterols and dietary phenolic compounds are known to provide cardio-protection via various mechanisms which includes reduction of prothrombic and inflammatory status and by improving endothelial function; phytochemicals are also known to modulate lipid profile and thereby provides protection against cardiac events (Golzarand et al. 2014; Craig 2010). Pathogenesis of atherosclerosis and neo-intimal thickening following angioplasty is associated with disproportionate migration and unregulated proliferation of smooth muscle cells (SMCs). In a combined set of experiments by Kesavan et al to show the anti-proliferative effects of *Gentiana lutea*, which is used in various drinks for its bitter flavor, along with its main component isovitexin revealed that aqueous root extract of *G. lutea* (1 mg/mL) and isovitexin (5 µM) inhibited PDGF-BB induced atherosclerosis associated proliferation of smooth muscle cells by downregulation of ERk1/2 and iNOS expression (Kesavan et al. 2013; Kesavan et al. 2016). Similarly, the anti-atherosclerosis effects and cholesterol-lowering effect of garlic might be attributed to the formation of allicin formed by the action of the enzyme alliinase on garlic (Sendl et al. 1992; Gebhardt and Beck 1996).

In vitro experiments also show the atherosclerosis reducing effects of polyphenolics of tea especially EGCG (0.1–3.0 µM) which was by retarding the invasion of SMCs mediated by attenuating MMP-2 activation and by increasing TIMP-2 levels. The SMC arrest is attributed to the blockage of cyclin D1 and cyclin E. Interaction of Tea polyphenols exert anti-proliferative effects by interacting with Matrix Metalloproteinases (MMPs) system. Induction and regulation of MMPs has been reported in a large number of processes involving tumor invasion, metastasis, angiogenesis, matrix proteins and tissue remodeling (Cheng et al. 2005). A recent investigation involving use of 3D co-culture of gingival fibroblasts and macrophages has suggested that green tea catechins (especially EGCG, 7.81–62.5 µg/mL), can be used as novel adjunctive treatment of periodontitis as these can decrease the secretion of MMPs that act as tissue destroying enzymes produced by immune and mucosal cells (Morin and Grenier 2017).

Thus, a very large number of elaborate and innovative in vitro studies have demonstrated exceptionally large number of health and therapeutic benefits of phytochemicals. Even the anti-atherogenic and anti-atherosclerotic activities of garlic were due to the reduction of lipid content and/or LDL oxidations by allicin present in garlic extract. The gamma-glutamyl cysteine component present in garlic might lower the blood pressure by inhibiting angiotensin-converting enzyme in vitro (Banerjee and Maulik 2002; Rahman, Biswas, and Kirkham 2006).

Ex vivo studies

Many previous Ex vivo studies have indicated that different types of phytochemicals are endowed with variety of biological activities including immuno-regulatory effects and antioxidant activity (Osakabe, Sanbongi, et al. 1998; Osakabe, Yamagishi, et al. 1998) and large number of recent studies concur with them. In the search for effective treatment for neovascularization mediated pathologies, nineteen pre-determined molecules were obtained from herbal extracts, and investigations for their anti-angiogenic effect showed that isoliquiritigenin, a chalconoid compound isolated from Chinese herb medicine licorice, potently inhibited vascular endothelial cell (EC) proliferation, migration and formation of tube -like structure ex vivo (Yang Wenxiao He 2014). *Theobroma cacao* L. contains appreciable amounts of 20 mg total phenol gallic acid equivalent per g of cocoa powder of phenolic substances such as epicatechin (Waterhouse, Shirley, and Donovan 1996). Holligan et al. (2014) have reported in their ex vivo techniques based study

that inclusion of pistachios in daily diet helps maintaining cholesterol of the body and have attributed this cholesterol lowering effect to a combination of β-sitosterol and fatty acid profile of pistachio diets (Holligan et al. 2014). Another interesting ex vivo study showed utility of kiwifruit that is rich in many phytochemicals, in preventive and therapeutic regime of cardiovascular disease as the kiwi fruit extract significantly inhibited the ex vivo platelet aggregation and plasma angiotensin-converting enzyme activity (Dizdarevic et al. 2014). Flavonoids upon evaluation for their ability to relax murine and human airway smooth muscles ex vivo showed galangin and fisetin (belonging to flavonol sub family) relaxing the acetylcholine pre-contracted murine tracheal rings and acetylcholine pre-contracted human airway smooth muscle strips significantly (Brown et al. 2016). In addition to previous in vitro studies, many previous ex vivo studies have also shown that plant sterols and stenols shift T helper (Th1)/Th2 balance to a Th1 type immune response that could be useful in Th2 dominant diseases like allergies and asthma (Brull et al. 2016). Ex vivo binding assays along with other approaches applied in the study done by Sun et al. (2017) has shown artocarpin, a bioactive compound present in *Artocarpus heterophyllus* (Jackfruit) to be potent colorectal cancer chemo-protective agent as it directly targets Akt 1 and 2 kinase activity (Sun et al. 2017). Thus, it becomes quite obvious that many ex vivo studies based evidences are there in the literature showing a wide variety of therapeutic effects of different phytochemicals that must be further harnessed to develop medicines and decoctions beneficial in gaining good health.

In vivo studies

Many in vivo and epidemiological studies significantly support the health benefits and therapeutic effects of phytochemicals. In this regard, many early and recent attempts can be quoted. For instance, Epidemiological studies have significantly highlighted that supplementation of tomato extract (containing carotenoid, lycopene) controls risk of hyperlipidemia, CVD, metabolic syndrome by regulating several physiological phenomenon like reduction of blood pressure of low density lipoprotein oxidation, and hypertension (Li and Xu 2013). A recent example supporting the health effects of carotenoids is a study that showed potential protective effects of four non-provitamin A carotenoids (lutein, lycopene, zeaxantin and astaxanthin) against metabolic disorders like diabetes and associated microvascular complications as these have capacity to quench free radicals, modulating gene expression and reducing inflammation (Murillo and Fernandez 2016). Phytochemicals such as phytosterols, organosulfur exhibit protective effect against atherosclerosis by regulating the levels of serum total and LDL cholesterol. Phytosterols such as sitosterol, campesterol, and stanols also induce cholesterol-lowering effect in both animal and human studies. Plant sterols are also known to exert anti-inflammation, anti-atherosclerosis and antioxidative activities (Berger, Jones, and Abumweis 2004).

According to study by Pelletier and coworkers, consumption of 0.7 g of soy sterols fed to 12 normal cholesterolemic individuals reduced LDL cholesterol by 15.2% relative to the control (Pelletier, Kundrat, and Hasler 2003). Observations from previous epidemiological studies have shown that supplementation of soy isoflavones for extended durations improve arterial compliance in men and postmenopausal women (Mahn et al. 2005). In a double double-blind, randomized, cross-over trial on oral trans-tetrahydrodaidzein which is normally formed after consumption of isoflavones (like daidezein), reduced blood pressure and central arterial stiffness indicating reduced cardiovascular risk (Nestel, Fujii, and Zhang 2007).

The molecular events behind the hypolipidimic effects of phytochemical have been profiled from studies on various in vivo models. Oryzanol, from rice bran oil (composed of phytosterols and ferulic acid) is considered a hypolipidermic agent as it has been found to eliminate bile acids and thus bring down the lipid profile in rat models (Bhaskaragoud et al. 2016). Further, in vivo studies on aged male rats have shown that supplementation of genistein and daidzein rich soy protein diet shows interaction with estrogen receptors, increased mRNA levels of eNOS and antioxidant enzymes (Mann et al. 2007). Furthermore, Aggarwal and Harikumar reported that oral application of 70–100 mg/Kg curcumin reduced systemic (plasma) and tissue specific inflammatory response, LDL oxidation and hypocholesteromic effects in rodents. Even the anti-atherogenic and anti-atherosclerotic activities of garlic were due to the reduction of lipid content and/or LDL oxidations by allicin present in garlic extract. The gamma-glutamyl cysteine component present in garlic might lower the blood pressure by inhibiting angiotensin-converting enzyme in vitro (Banerjee and Maulik 2002; Rahman, Biswas, and Kirkham 2006).

Phytochemicals also provide promising protection against diabetes associated damages. In a long term study on isoflavones and flavan-3-ols against CVD in type 2 diabetic postmenopausal women aged between 51 to 74, flavonoid consumption (27 g/day, consisting of 90 mg epicatechin (850 mg total flavan-3-ols) and 100 mg isoflavones (aglycone equivalents), along with regular statin therapy reduced the LDL-cholesterol levels (C) and total-C:HDL-C ratio significantly. Analysis after 6 months and 12 months showed that, flavonoid intake caused an increase in total epicatechin and isoflavone amounts in 24-h urine. The treatment ameliorated insulin resistance following significant reduction in insulin levels. The intervention showed a significant effect in reducing chronic heart disease risk from 1.1% in the placebo group to 0.1% in the treatment group (Curtis et al. 2012). Similarly, data from 3 prospective cohort studies, the amount of flavonoid intake was correlated with reduction in type 2 diabetes. Consumption of anthocyanin rich foods like blueberries, strawberries, apple showed significant reduction in diabetes risk irrespective of their source (Wedick et al. 2012). A recent investigation involving randomized, double blind, placebo controlled trial showed that upon supplementing with garlic extract, the endothelial biomarkers related to cardiovascular risk are modified and chronic inflammation is suppressed in obese individuals (Szulinska et al. 2018).

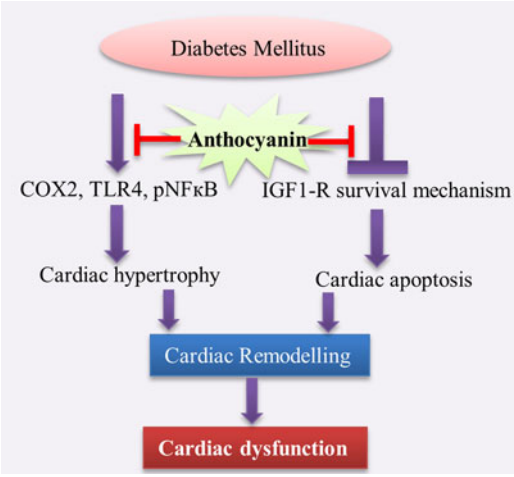

Figure 1. Anthocyanin intervention suppressed the cardiac fibrosis associated inflammatory mediators and enhanced the IGFI-R/Akt survival mechanism in the left ventricles of diabetic hearts.

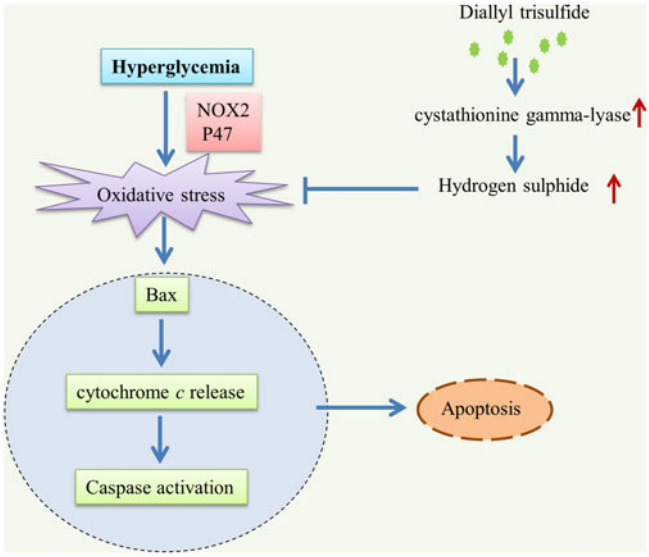

Figure 2. H2S plays prominent role in diallyl trisulfate mediated IGF1 R/Akt-mediated cardioprotection against diabetes associated damages.

Experiments in animal models also provide strong evidence for the antidiabetic effects of phytochemicals. Total flavonoids from *Selaginella tamariscina* has been shown to be effective against diabetes-associated hyperglycemia. Administration of around 200 and 400 mg/kg/day of flavonoids from *S. tamariscina* in STZ induced diabetes rats show increased PPARγ protein expression, which is related to insulin sensitivity, by 24% and 30%. *S. tamariscina* flavonoids also increased IRS-1 protein by more than 85% in diabetic rats (Zheng et al. 2011). Likewise, based on animal experiments, fenugreek seed has also found to be effective for treatment of diabetes with soluble fiber as its main active components that help in decreasing post-prandial glucose (Graf et al. 2010). Clinical trial with a food formulated containing 10% fenugreek seed enhanced glucose tolerance by >20% in both diabetic as well as in non-diabetic patients in 2 weeks (Srinivasan 2006). A significant reduction in blood pressure in salt-sensitive spontaneously hypersensitive rats was found following supplementation with 3% blueberry enriched diet for 8 weeks (Kalea et al. 2009). Hypoglycemic effect of blueberry has been attributed to the presence of anthocyanin (Bell et al. 2017).

In an earlier study in type 2 diabetes KK-A(y) mice models show that feeding of 0.2% of cyanidin 3-glucoside diet for 5 weeks reduces hyperglycemia and insulin sensitivity by suppressing retinol binding protein 4 expression and enhancing the glucose transporter 4 (Sasaki et al. 2007). In a streptozotocin induced diabetes rat models oral administration of 250 mg/kg/day of purple rice anthocyanin isolates for 4 week ameliorated systolic dysfunction and enhanced the ejection fraction (%) and fraction shortening to attenuate diabetes associated cardiac remodeling. Anthocyanin intervention suppressed the cardiac fibrosis associated inflammatory mediators and enhanced the IGFI-R/Akt survival mechanism in the left ventricles of diabetic hearts (Chen et al. 2016; Huang et al. 2017); (Figure 1).

In a study in streptozotocin-induced diabetes mellitus, diallyl trisulfide a metabolite of garlic, provided protection against cardiac apoptosis by enhancing IGF1R/pAkt signaling which was correlated with reduction in the expression of reactive oxygen species-related enzymes NOX2. Further analysis show that diallyl trisulfide administration elevates plasma H_2S levels by enhancing cystathionine gamma-lyase, an enzyme responsible for tissue H2S production in mammals (Tsai et al. 2015); (Figure 2).

Furthermore, extracts of Russian tarragon also possess strong antihyperglycemic/antidiabetic potential in streptozotocin induced genetically diabetic KKAy murine models (Berger, Jones, and Abumweis 2004). Nonetheless, the, antihypertensive effect of garlic extract was also evaluated both in hypertensive rats and in controlled human (hypertensive) studies. The hypolipidemic effect of resveratrol was found to exert a significant reduction of serum total cholesterol, triglycerides and lipid content in hepatic tissue in high-fat diet hamster. Impaired metabolism and overproduction of ROS also contribute to wide variety of neuronal degenerative diseases and onset of neuronal diseases such as Alzheimer's disease (AD) and Parkinson's Diseases (PD). Studies with transgenic mouse model of AD showed that supplementation of curcumin reduces neuronal oxidative stress by inducing the expression of cyto-protective proteins or antioxidant enzymes such as superoxide dismutase (SOD), glutathione reductase (GR), Catalase, glutathione peroxidase (GPx), heme oxygenase-1 (HO-1), and glutathione-S-transferase (GST) (Lim et al. 2001; Dickinson et al. 2003). Furthermore, administration of resveratrol to transgenic mouse model of AD have shown its protective role against neuronal impairments via inhibition of NF-kB modulated expression of several pathways

Drion et al. (2018) have studied anti-epileptic effect of intra-cerebrally applied curcumin in the post-electrical SE rat model for temporal lobe epilepsy and observed the modulation in MAPK pathway in vivo but not eliciting its usual anti-inflammatory and anti-oxidant effects (Drion et al. 2018). In addition to its therapeutic usage in jaundice, lung cancer wound healing, there is a possibility of its use in treatment of neuro-degenerative disorders as it is found to modulate redox status and mitochondrial dysfunction

(Chandran and Muralidhara 2013, 2014; Drion et al. 2018). They have concluded that more research should be directed to increase the bio-availability of curcumin in brain so that its anti-epileptogenic effect can be assessed. Moreover, the neuro-protective effects of blue berries and lignoberries have been recently reviewed by Kelly et al. (2017) and the effects were attributed to their antioxidant efficiency of flavonoids (Kelly, Vyas, and Weber 2017). An interesting finding has been the neuromodulatory propensity of *Selaginella delicatula* by in vivo models of chemically induced neuro-degenerative diseases in drosophila and rodents (Chandran and Muralidhara 2013).

A Study conducted by Aviram et al., with human subjects, reported a significant decrease in lipid peroxidation in plasma following consumption of pomegranate juice (PJ, 50 mL/day) for 2 weeks. Moreover, a remarkable rise in plasma total antioxidant status was also found after 2wks of consumption of PJ. Altogether, the study observations concluded that daily consumption of PJ may reduce the progression of atherosclerotic lesion. Some of the phenolic compounds such as ferric acid, chlorogenic acids and a plant alkaloid berberine, have potent anti-diabetic action with high therapeutic efficiency and lesser side effects. Nutraceuticals like berberine, curcumin and resveratrol regulate the PI3K/PTEN/Akt/mTORC1/GSK-3 pathway through multiple mechanism such as micro-RNAs, ROS etc. and thus act as therapeutics against many diseases like diabetes, cancer, hyperlipidemia and bacterial infections (McCubrey et al. 2017). Another evidence for in vivo experimentation showed that polyphenolic rich tea flower extract possess anti-inflammatory effect against chronic inflammation associated with significant reduction of tissue specific (liver) acute inflammation by blocking cytokines (TNF-alpha, IL-1β) expression and NO production. Supplementation of curcumin as oral gavage in male mice significantly reduced systemic inflammation by preventing the release of TNF-α and C-reactive protein (CRP) In separate studies, Oral consumption of cinnamon bark extract and its polyphenol (procyanidine) regulated the systemic inflammation by regulating CRP levels and stimulating autoimmune system.

A wealth of evidences report numerous epidemiological studies reporting significant reduction of plasma cytokine levels, CRP in healthy individuals after consumption of rye bran and whole wheat bread with the possible explanation that the short-chain fatty acid of cereal fiber prevents inflammatory response in colonic mucosa by binding to the G-protein coupled receptor and by blocking transcription factor NF-κB. Hypoglycemic effect of blueberry extract found in humans was attributed to the presence of anthocyanin and myrtillin. A significant reduction in blood pressure in salt-sensitive spontaneously hypersensitive rats was found following supplementation with 3% blueberry enriched diet for 8 weeks (Kalea et al. 2009; Kalea et al. 2010). Furthermore, extracts of Russian tarragon also possess strong antihyperglycemic/antidiabetic potential in streptozotocin induced genetically diabetic KKAy murine models (Berger, Jones, and Abumweis 2004). Nonetheless, the, antihypertensive effect of garlic extract was also evaluated both in hypertensive rats and in controlled human (hypertensive) studies. The hypolipidemic effect of resveratrol was found to exert a significant reduction of serum total cholesterol, triglycerides and lipid content in hepatic tissue in high-fat diet hamster. As per reports of Khan et al., administration of green tea polyphenol (e.g., EGCG) in transgenic adenocarcinoma mice produces a significant inhibition of cancer progression or metastasis of prostrate tissue by regulating MMP 2 and MMP 9 expression (Moore et al. 2008). The wound healing capacity of *Tephrosia purpurea* studied in rats bearing different typesof wounds. Following treatment of wound area with *T. purpurea* ethanolic extract showed increase in angiogenesis, fibroblast formation and collagen fiber generation due to presence of flavonoids in the extract (Lodhi et al. 2006). In vivo murine study done by Brown et al. (2016) demonstrated that inhaled galangin attenuated the increasing lung resistance due to methacholine, a muscarininc receptor ligand that is used to diagnose bronchial hyperactivity (asthma, chronic obstructive pulmonary disease) (Brown et al. 2016). Withaferin A, a steroidal lactone obtained from *Withania somnifera* (Ashwagandha), *Acnistus arborscens* and other members of the Solanaceae family, has remarkable anti-cancer activity by restoring the tumor growth suppressor function of Notch2 in triple negative breast cancer cells. Apart from these evidences, thousands of other studies have reported the therapeutic applications of phytochemicals. Figure 3 summarizes the major pathways that are modulated by different phytochemicals.

Problems associated with the usage of phytochemicals

Toxicity

There are numerous toxic effects reported from well-known phytochemical and their source. Reserpine, a known dopamine inhibitor is extracted from *Rauwolfia serpintina* or *Rauwolfia vomitoria*, has been clinically used to control hypertension, schizophrenia, insomnia and insanity. This drug usage has been limited due to its side effects oxidative damage to organs, including the liver (Al-Bloushi et al. 2009). Intra muscular dose of reserpine in hypertension patients showed higher toxicity than oral doses, however opposing reaction was found in patients who have not received *Rauwolfia* derivatives prior to admission (Pfeifer, Greenblatt, and Koch-Wester 1976). Emetine dihydrochloride is derived from the root of *Carapichea ipecacuanha* and used an anti-protozoal drug (Matthews et al. 2013). Though it is a potential intestinal and tissue amoebicide drug its use has been restricted due to its side effects like nausea and vomiting. Similarly, higher doses required for tissue amoebicidal activity showed cardiotoxic effects in a amount of the patients treated (Matthews et al. 2013).

Pyrrolizidine alkaloids have been receiving greater attention as they are distributed in plants and other sources of human and animal nutrition such as honey, milk offal and eggs. (Moreira et al. 2018). Long-term exposure to low levels of pyrrolizidine alkaloids via food intake yields chronic VOD which leads to liver cirrhosis. Other than liver,

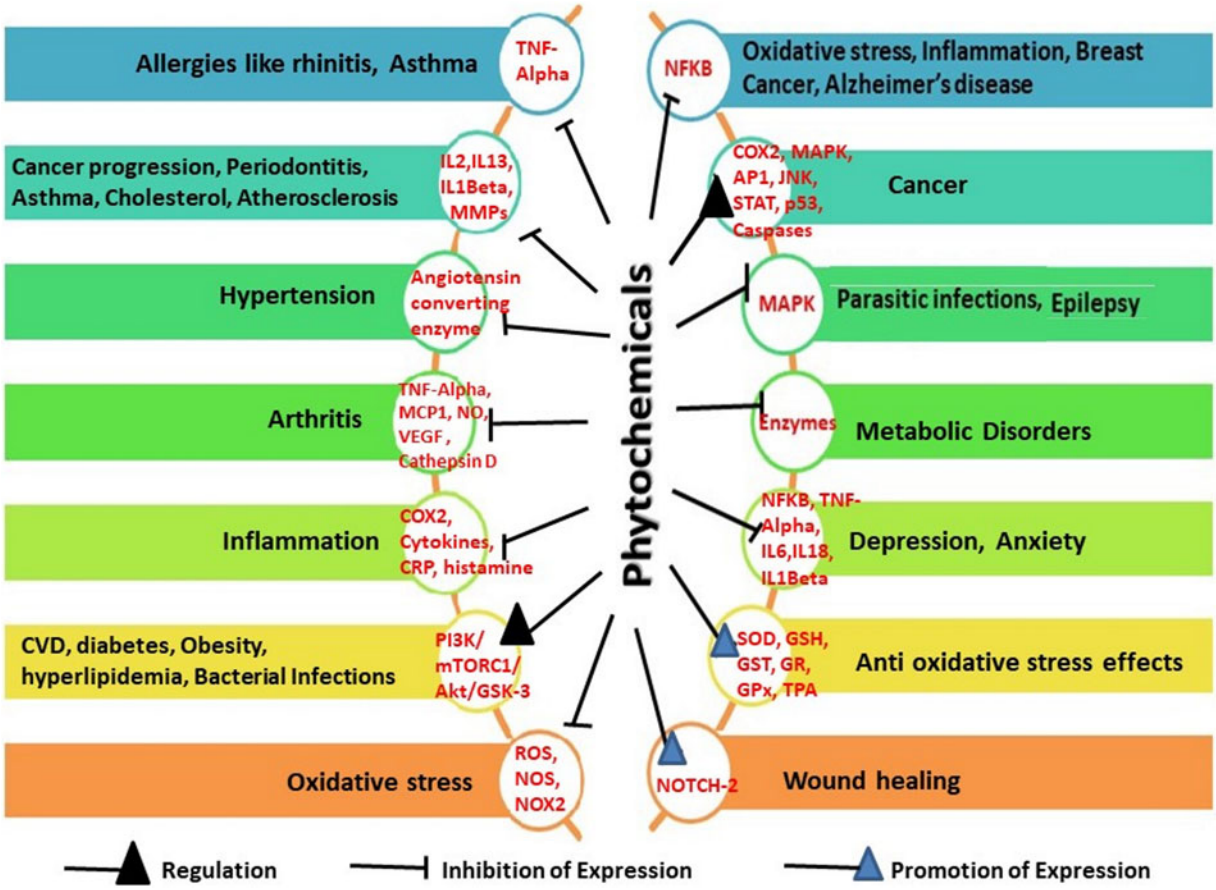

Figure 3. Therapeutic molecular targets of phytochemicals and the diseases they fight off.

lungs (pulmonary hypertension) and the cardio-vascular system (cardiac right ventricular hypertrophy) can be affected too (Koleva et al. 2012). Tropane alkaloids are found in high concentration in dietary plants of *Solanaceae* and *Erythroxylaceae* families. Several Tropane alkaloids are however, known to be hallucinogenic and few are strong anticholinergic drugs. Tropane alkaloids such as Atropine, hyoscyamine and scopolamine are known anticholinergics due their antagonistic action on muscarinic acetylcholine receptors [43]. Their side effects include dryness of the mucosa of the upper digestive and respiratory tract, constipation, pupildilatation and disturbance of vision, photo-phobia and dose-dependent occurrence of hyper-orhypotension, bradycardia or tachycardia as well as arrhythmias, nervousness, restlessness, irritability, disorientation, ataxia, seizures and respiratory depression [32]. *Piper nigrum*, also known as black pepper contains 5–9% (50–90 g/kg) piperine [50]. Daily consumption of 0.33 g of black pepper by a 60 kg person. Several cases of fatal pepper administration have been reported in the literature [53, 54]. Jellin and Gregory (2007) have found that white and black pepper is unsafe to pregnant women and young children when consumed in large amount amounts.

Bioactive isolates

It is a well-known fact that crude plant extracts often contain various types of bioactive compounds. Despite the fact that plant extracts usually occur as a combination of various types of bioactive compounds their preparation remains a big challenges. The type of extraction process needs to be chosen meticulously as inappropriate selection of method and source of sample may produce alterations in the content. For instance comparison between fresh and dried *Moringa olifera* leaves showed no substantial effect in total phenolics but higher flavanoid content in dried samples (Vongsak et al. 2013). Methods such as pre-extraction preparation of plant sample such as air-drying, are time-consuming and may be subject to contamination at unstable temperature condition. Microwave drying which uses electromagnetic radiations may sometimes cause degradation of phytochemicals (Kaufmann and Christen 2002).

Oven drying uses thermal energy may influence bioactive components such as sinensetin and rosmarinic acid affected in case of "Orthosiphon stamineus" (Abdullah, Shaari, and Azimi 2012; Mediani et al. 2013). For extraction techniques such as maceration, infusion, percolation and decoction involve the issue of organic waste as large volume of solvents, is used and proper management of waste is required (Abdel-Azim et al. 2013; Yung, Maskat, and Mustapha 2010). Method of Soxhlet extraction requires small volume of solvent however; disadvantage is that exposure to hazardous and flammable liquid organic solvents with potential toxic emissions during extraction. Solvent requirement may also add to cost (Naude et al. 1998). Microwave assisted extraction have reduced times but requires proper training

and caution of using proper conditions to avoid thermal degradation and method is limited to small phenolic compounds. Sometimes yield is also affected (Kaufmann and Christen 2002). Ultrasound assisted extraction (USE) method involves a reduction in extraction times and solvent consumption occurs but use of USE may have an effect on active phytochemicals through the formation of free radicals (Yingngam, Monschein, and Brantner 2014). The Accelerated solvent method (ASE), is although an efficient form of liquid solvent extraction method compared to other method but highly dependent upon the type of solvent. Supercritical Fluid Extraction (SFE) is an optimum yield giving method with reduced extraction times however initial cost of equipment is very high (Naude et al. 1998; Patil et al. 2014). Conventional techniques like TLC have been used to extract nutraceuticals from *Spirulina*, the blue green algae of high nutritive value (de Laguna et al. 2015) while some others have used novel techniques like ultrasonic assisted dynamic extraction coupled with countercurrent chromatography to extract compounds like maackiain, genistein, prunetin, irilone and diadzein of more than 95.31% purity from red clover (Zhang et al. 2015). With application of advanced extraction procedures, more and more underutilized plants have come under the category of medicinally and nutritionally useful (e.g., *Salacia chinensis* L (Ghadage et al. 2017). However, there are many challenges in this field and a large number of factors govern successful and viable extraction of phytochemicals and other metabolites from plants. Altogether, evaluation, selection and pre-extraction preparation and extraction methodsdepend upon study objectives samples and target compounds. In other cases, it has not been possible to isolate active constituents from active extracts. Several explanations have been proposed for this, such as the poor quality of ethno-pharmacological studies, plant material processing, pre-clinical laboratory protocols which are often very different from local practices, an inadequate fractionation process, degradation of active constituents during fractionation and poor biological models for demonstration purposes (Rasoanaivo et al. 2011). Also, there is enzymatic degradation of the obtained compounds depending on the method of extraction used (Bijttebier et al. 2016). Further, pure drugs that are industrially produced or isolated from plants rarely have same degree of activity as the unrefined extract at comparable concentrations or dose of the active component due to absence of interacting substances present in the extract. Often pure drugs are more expensive to produce and distribute and so are mostly unavailable to the poorest populations in remote areas who need them most. Bijttebier et al. (2016) have elaborated on another aspect related to plant metabolomics studies that none of the extraction methods used in their study allows exhaustive extraction of the metabolites and there is low resolving power for phytochemicals for all the methods (Bijttebier et al. 2016).

Combinatorial phytochemistry: The pros and cons of synergism

To overcome the difficulties in isolating a single active ingredient, the concept of synergistic interactions plays a vital role in phytomedicine. A whole or partially purified extract of a plant offers advantages and also underpins the philosophy of herbal medicine. Combinatorial methods have been implemented to synthesize medium-sized and large-sized libraries that enable diverse modifications of the active compounds. These combinatorial approaches are useful for screening number of active compounds and to elucidate the mode of action of the compounds as well as biological target (Jung, Glaser, and Brase 2013). In recently published report, most efficacious treatment for prostate cancer was identified. Ursolic acid, curcumin and resveratrol were administered in vivo via the diet either in combination or alone and the combinations produced synergistic effects on size of tumors and their effect on the targets viz. ASCT2 levels, STAT3, mTORC1 and AMPK activity were modulated to a greater extent by the combinations compared to individual components. Such combinatorial approach has been found useful in identifying synergistic combinations of natural compounds for chemo preventive and therapeutic interventions (Lodi et al. 2017). It is widely accepted that health benefits of diets rich in fruits and vegetables in reduction of risk for chronic diseases (like cancer) are not exclusively due to specific phytonutrients but due to combinations such as carotenoids with retinoic acid and active metabolite of vitamin D or combination of several carotenoids like lycopene, phytofluene, phytoene; or carotenoids with poly phenols (like curcumin, carnosic acid) etc. (Linnewiel-Hermoni et al. 2015). Chiou et al. (2018) have also suggested that for treatment and prevention of breast cancer, combination therapy with phytochemical diet supplementation is most promising as it enhances the efficacy, minimizes side effects of radio- and chemo-therapy and overcomes multidrug resistance (Chiou et al. 2018). Synergistic effects are also reported among combination of phytochemicals with secretory products of microbes and this can be a very useful approach to get variety of "hybrid" therapeutic agents. Another in vitro study has reported synergism in activity from sequenced combinations of mono-functional platinum tris (benzimidazole) mono-chloro-platinum (II) chloride with quercetin, cisplatin, capsaicin, and curcumin in both, parent cancer cell line (A2780) and resistant cell lines (A2780(cisR) and A2780(ZD0473R)) (Arzuman et al. 2014). Another interesting study reported effective antimicrobial activity and strong synergistic interaction of phenolic rich maple sirup extract with specific antibiotics that act against clinical strains of Gram negative bacteria like *E. coli, P. aeruginosa* and *P. mirabilis* (Maisuria, Hosseinidoust, and Tufenkji 2015). The synergistic effects have although been considered to be positive with low doses usage as a benefit, however, it elicits a negative impact also. The most apparently observed effect is adverse reaction (ADR'S) occurring with combinations of herbs or between drug-drug interactions. For instance, presence of tannins in herbal drugs is an unwanted interaction which may hinder absorption of alkaloids and proteins or induction of drug metabolizing enzymes such as cytochrome P450 which eventually results in low levels of actives in the blood, a concentration too low to produce a therapeutic effect (Williamson 2001). Besides, synthetic drugs are also

known to possess interactions with herbal drugs and patients taking them are warned before prescription (Ernst 2005; Fasinu, Bouic, and Rosenkranz 2014). Some of the examples are cyclosporins, warfarin. Furthermore, herbal products with significant synergistic potential should not be used if they are potent herbs used in conditions where dose is crucial. Although phytochemicals are extracted from natural plants are generally nontoxic, but they can confer their toxicities to human systems at certain situation (drug-drug interaction) and concentration which hinder their application in clinical studies and future application in chemoprevention and treatment (Williamson 2001).

Bioavailability is a major challenge that needs to be overcome for many phytochemicals (Table 2). For example, curcumin shows low bioavailability in earlier studies. Dosing of phytochemicals via oral route in the form of supplements may show low bioavailability due to excessive metabolism by Phase I and Phase II drug metabolism enzymes (DME). The same may hamper the phytochemicals from being available for absorption and distribution in the body. Phase I drug metabolism enzymes include mostly cytochrome P450 and can be found in most tissues of the body. They are involved in reduction, oxidation or hydrolysis to increase the polarity of a drug (Hoensch and Oertel 2011). An important aspect of phytochemicals is their ability to act via CYP enzymes. Famous examples include grapefruit juice that inhibit CYP3A4 mediated metabolism of certain drugs and cause the increased bioavailability of the drug and potential toxicity. Some other examples are watercress inhibiting CYP2E1 which may complicate the absorption of some drugs. Therefore, phytochemicals have to be studied further for such effects (Bailey and Dresser 2004; Leclercq, Desager, and Horsmans 1998; Wang et al. 2012). To improve bioavailability, liposomes, micelles and nanotechnology have been used (Eisenstein et al. 2010). Not only this, the crystal structure of phytochemicals, amorphism, polymorphism, should also be taken into account for development of a drug since physical forms of a phytochemical may impact the solubility, adsorption, variation in pharmacokinetic performance, product content consistency in large scale manufacturing, degradation product formation and pathway during product storage (Clas 2003).

Chemically modified phytochemicals and nanotechnology: Recent approaches to bolster phytochemicals as therapeutics

It is thus clear from the above section that despite the important role of phytochemicals in prevention of a number of diseases challenges are associated with their proper administration in the body because of their low solubility, low absorption and bioavailability and issues related to their half- life of orally administered phytochemicals. To overcome these issues chemical engineering strategies have been employed such as chemically modified phytochemicals and development of nanotech based phytochemicals. These chemically engineered phytochemicals possess improved cellular permeability, stability and increased half-life of cells. In pursuit of increasing the accessibility of phytochemicals, AbBF4- has proved to be an efficient tool owing to its ability to complex with and activate electron rich atoms and bonds under mild conditions (Donno et al. 2016). Similarly, conjugation of curcumin (CCM) by Poly ethylene glycol (PEG) has been developed to improve its solubility. Cellular uptake kinetics of natural form of CCM and CCM-PEG revealed that improved water solubility of CCM-PEG was correlated to higher cellular retention in CCM in 3T3-L1 cells, with predominant effect in preadipocytes (Kim et al. 2011). Further investigations with inhibitory role of CCM-PEG also suggested that pegylation mediated improved water solubility and cellular retention may prove beneficial in improving the delivery of CCM in preadipocytes and its antiadipogenic ability (Kim et al. 2011). Another strategy is bioconversion where phytochemicals are converted in to some high value compound, for instance, Josefsen et al. (2017) bioconverted phytosterols in to androstenedione using *Mycobacterium* spp. (Josefsen, Nordborg and Sletta 2017). Chemically modified flavonoid-phytochemicals have been synthesized that have antibacterial activity against *M. tuberculosis*, methicillin resistant *S. aureus* by mechanisms like dissipation of bacterial membrane potential, inhibition of DNA topoisomerase IV (Feng et al. 2014). More recent approaches to better optimize the formulations of natural products like polyphenols and for subsequent successful therapeutic effects involve use of computational tools instead of wet lab experiments for tasks like selection of drug-carrier pairs (Metwally, El-Ahmady, and Hathout 2016). To improve the delivery of certain phytochemicals use of nanoparticles has made available. As in case of Thymoquinone (TQ) is a quinone-based phytochemical present in *Nigella sativa* (*ranunculaceae*) its administration remains poor due to poor water solubility and administration of high dosages to rats resulted in hypoactivity and difficulty in respiration associated with reduced glutathione in liver and kidney (Cho et al. 2011). Reports have shown that TQ was capable of reducing blood glucose levels and induction of allergic dermatitis. To overcome these limitations, biocompatible and biodegradable polymeric nanoparticles has been proposed as attractive alternatives for TQ delivery with improved solubility, controlled delivery and enhanced therapeutic properties (Ballout et al. 2018). Further, to improve the bioavailability, stability and solubility of polyphenols like quercetin, curcumin and resveratrol, for maximizing their anticancer activity, formulations using nanoparticles have been prepared that have more targeted activity at the tumor (Bonferoni et al. 2017). In case of curcumin also it has been observed that despite curcumin have widespread clinical application in cancer and other diseases, it has limited activity due to poor aqueous solubility and consequently minimal systemic bioavailability. Nanoparticles based approaches render hydrophobic agents like curcumin dispersible in aqueous media. Polymeric nanoparticle encapsulated formulation of curcumin –nanocurcumin have been synthesized-using the micellar aggregates of cross-linked and random copolymers of Nisopropylacrylamide (NIPAAM), with N-vinyl-2-pyrrolidone (VP) and poly (ethyleneglycol) monoacrylate (PEG-A)

Table 2. Bioavailabity of phytochemicals.

S. No.			Quantity ingested	Maximum Blood concentration (Cmax)	Peak concentration in blood (Tmax)	Predicted absorption	Excretion in urine	References
1	Nicotine	Tobacco	Oral capsule Oral solution (45 mg/kg)	6–8 ng/mL 2.9 ng/mL	90 minutes 66 minutes	44% 20%	5%	Benowitz and Jacob (1998) Benowitz, Hukkanen, and Jacob (2009)
2	Caffeine	Coffee	Oral solution (5 mg/kg) Oral coffee consumption Oral Coffee product (71 mg)	10 µg/mL 2.47 µg/mL 10 µM	30 min 45 minutes 80 minutes	97% 67%		Teekachunhatean et al. (2013) Martínez-López et al. (2014)
3	Quercetin	Onion Apple Blackwheat tea	68 mg 98 mg 200 mg	224 ng/mL 92 ng/mL 0.64 µg/mL	42 minutes 150 minutes 258 minutes		1.39% 0.44% 0.8%	Hollman et al. (1997) Graefe et al. (2001)
4	Epigallocatechin gallate	Green tea infusion Green tea	88 195 ng	0.33 µM 78 ng/mL	96 minutes		3.3%	Lee et al. (2002)
5	Epicatechin	Whole apple puree	70 mg	2.1 µM	102 minutes	44.3%	29%	Hollands et al. (2013)
6	Catechin	Red wine	34 mg	0.072µM				Donovan et al. (1999)
7	Genistein	Soy milk	19 mg	0.74 µM		9%	19.8%	Xu et al. (1994)
8	Naringin	Grapefruit extract Orange Juice	43 mg 23 mg	<4 µM 16 µg/L	276 minutes	0.1–0.4	8.8% 7.1%	Fuhr and Kummert (1995) Manach et al. (2003)
9	Naringenin	Grapefruit juice Orange Juice	199 mg 23 mg	1628 µg/L 175 µg/L	288 minutes 330 minutes		30.2% 1.1%	Erlund et al. (2001)
10	Hesperetin	Orange Juice	126 mg	655 µg/L	324 minutes		5.3%	Erlund et al. (2001)
11	Anthocyanins	Red wine Red grape Juice Concentrate	279.6 mg 283 mg	42.9 ng/mL 100.1 ng/mL	90 minutes 30 minutes		0.18% 0.23%	Bitsch et al. (2004)
12	Chlorogenic acid	Mango flesh Mango Juice	17.96 mg 7.32	49.7 ng/mL 109.7 ng/mL	210 minutes 150 minutes			Quirós-Sauceda et al. (2017)
13	Protocatechuic acid	Mango felsh Mango Juice	0.4 mg 0.53	30.8 ng/mL 34.5 ng/mL	210 minutes 222 minutes			Quirós-Sauceda et al. (2017)
14	Ferulic acid	Mango felsh Mango Juice	1.94 mg 1.59	16.5 ng/mL 32.7 ng/mL	168 minutes 138 minutes			Quirós-Sauceda et al. (2017)
15	Gentisic acid	Mango felsh Mango Juice	0.24 0.18	11.8 ng/mL 12.2 ng/mL	240 minutes 168 minutes			Quirós-Sauceda et al. (2017)
16	Gallic acid	Mango felsh Mango Juice	16.52 15.9	8.7 ng/mL 7.9 ng/mL	264 minutes 210 minutes			Quirós-Sauceda et al. (2017)
17	Resveratrol	Red Wine		0–2.7 µM	30 minutes			Smoliga and Blanchard (2014)

(Bisht et al. 2010). Nanocurcumin, unlike free curcumin, is readily dispersed in aqueous media and show therapeutic efficacy to free curcumin against a panel of human pancreatic cancer cell lines (Bisht et al. 2010). Nano-emulsions have been developed to deliver pomegranate polyphenols in the deeper layers of skin (Baccarin and Lemos-Senna 2017). Pimentel-Moral et al. (2018) have also reported in their review that lipid nano-carriers used commonly to encapsulate polyphenols enhances their bioavailability and bioactivity along with decreasing the eventual side-effects and modifying their release profile (Pimentel-Moral et al. 2018).

Alkaloids with many reported useful aspects also have many associated limitations that have been in the process of being addressed to enhance the therapeutic applicability of these compounds. Nanotechnology has been utilized in this regard also. For instance, recently, a novel nano-lipid approach that is based on elastic phospholipid vesicles has been used to encapsulate a semi-purified extract of capsicum (Bhut jolokia) fruit for topical application drug delivery application (Sarwa et al. 2016). This was done to reduce its concentration-dependent irritation and it has been found to be acceptable upon testing in human volunteers in a phase 1 clinical trial (Sarwa et al. 2016). Another very recent example is that of berberine whose limitations like poor aqueous solubility, low absorption and bioavailability have been overcome by developing nano-carriers (polymer based, lipid based, magnetic mesoporous silica based, graphene based, gold and silver nanoparticles) to encapsulate it (Sarwa et al. 2016). Nano-technological advances have also taken place involving use of sulfated polysaccharides from natural sources like plants and animals along with the synthetic ones due to their biocompatibility and biodegradability that facilitate nano-particle synthesis and tissue engineering application (Raveendran et al. 2013). These polysaccharides have been used in stabilization, cross-linking, ionic gelation, capping and encapsulation of drugs (Raveendran et al. 2013). Mertaniemi et al. (2016) have suggested that glutaraldehyde cross-linked threads of nano-fibrilated cellulose upon association with human adipose mesenchymal stem cells is an effective surgical biomaterial to ward off post-

operative inflammation and chronic wound-healing issues (Mertaniemi et al. 2016). Dumanli (2017) has reviewed the biomedical and other applications of nanocelluloses and suggested that these are very cost effective and advanced materials for such areas due to their low cytotoxicity, biodegradability and biocompatibility (Dumanli 2017). Not only this, their chemical functionality can be very easily altered to yield many useful products and also find application in many fields like tissue engineering, drug delivery, diagnostics, medical implants, wound healing, 3D printing and magnetically responsive materials (Dumanli 2017). Nanotechnology based advanced molecules like nanocarriers, nanovectors, nanoparticles, nanoemulsions for essential oils (EOs) have been developed for specific purposes. For instance, nano-encapsulated thymol and carvacrol EOs have been developed using a prolamine protein called zein found in maize (Wu, Luo, and Wang 2012). Another recent work done by Bizzarro et al. (2016) showed preparation of cumin and basil oil loaded polyamide capsules that can release their cargo oil upon irradiation with (Bizzarro et al. 2016).

Future perspectives

Aromatic and medicinal plants produce secondary metabolites that have extensive uses as fragrances, flavoring agents, dyes, insecticides and drugs. Biotechnology has many innovative ways to offer through which their useful products like phytochemicals can be overproduced while reducing the toxic content and even produce novel chemicals (Gandhi, Mahajan, and Bedi 2015). For example, biotechnological approaches have been utilized to produce recombinant cystatins that are highly effective against pests (Martinez et al. 2016). New areas of application of phytochemicals with increased effectiveness have been searched and it is quite possible that in near future, such novel products shall be available which would be able to do things that have been quite challenging since the beginning. For instance, many new phytochemicals (like L-theanine from green tea, matairesinol and lignins arctigenin from *Arctium lappa* seeds) have been reported that exhibit anti-aging effects (Correa et al. 2018). Phytochemicals being integral components of herbal medicine gained popularity by virtue of their ability to modulate signal transduction mechanism and cellular responses to pathogenic stimulus. Several in vitro, in vivo, preclinical as well as epidemiological studies have demonstrated their therapeutic actions. Although, with extensive mechanistic studies the therapeutic potential of phytochemicals have come into action, future investigations are still required to thoroughly understand their performance, pharmacodynamics, pharmacokinetics, metabolism, toxicities, formulation, dosage regimen to exploit them as therapeutics in phytomedicine. Despite their preventive role in a number of diseases there are some challenges associated to them like dosage regimen, solubility, synergistic effects, and poor half-life. Future investigations are required to ensure high yield, viability and better solubility. Further, some of the antioxidant activities of natural compounds demonstrated in vitro studies are not reproducible in vivo. At some occasions natural phytochemicals demonstrate hepatic and gastrointestinal toxicities. Therefore, a thorough understanding of the compounds and their pharmacological effects is still essential for natural phytochemicals druggability and their transition from bench top to patient's bedside.

Conflicts of interest

The authors have declared that no competing interests exist.

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