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Review Article

Cancer-Fighting Phytochemicals: Another Look

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ABSTRACT

Plant chemicals, known as phytochemicals present in a number of fruits, vegetables, greens, herbs, and marine organisms, algae, seaweed, and sponge contain large amount of bioactive compounds/nutrients. They have various health benefits, including antioxidant, anti-cancer, antimicrobial, anti-inflammatory, anti-diabetic, and antibiotic properties. Today, researchers exploring the characterization of various traditional plants and plant constituents and marine organisms against a number of cancers, such as lung cancer and cervical cancer. There exists thousands of phytochemicals, which provide notable health benefits. Most spices, fruits and vegetables contain phytochemicals and their nutritional constituents are being intensively studied to evaluate their effects on health and cancer treatment. In this review, the phytochemicals, such as alkaloids, tannins, saponins, steroid, terpenoid, flavonoids, phenolic compounds, etc. in various fruits, medical plants, and marine red algae are screened and studied for their phytochemical components.

Keywords: Phytochemicals; Plant chemicals; Nutraceuticals

INTRODUCTION

The several million deaths due to cancer each year indicates that the current standard of cure with its chemotherapeutic drugs is inadequate. WHO informs that the global cancer rates could increase by 50% by 2020 more than 50% and the majority to get affected will be in in low and medium income countries, with lack of chemo drugs in addition to other resources [1]. There is an urgent need for alternate anticancer drugs. Targeting protein–protein interactions (PPIs) provides opportunities for new cancer therapies. Modulating PPI interfaces with organic molecules has been found to be challenging one, and few researches have successfully resulted in the development of new clinical drugs. The unique properties exhibited by metal compounds render an attractive support for the development of bioactive leads. The enantiomeric iridium (III) metal compound could potentially be used as starting scaffolds for the development of more potent Ras/Raf PPI inhibitors for the treatment of kidney cancer [2]. Benzofuran-conjugated iridium (III) complex has been used as an anti-prostate cancer agent [3]. Prolyl-isomerase 1 (Pin1), a conserved enzyme inhibitor blocks NF-kB signalling in prostate cancer cells [4]. Rhodium (III) Complex has been to inhibit proliferation of TP53-mutated Triple-negative Breast Cancer Cells [5]. Also, we can use natural phytochemicals from plants/herbs and other natural resources to treat cancer. Phytochemicals are fully loaded with nutraceuticals that have abundant anticancer properties. Figure 1 shows an illustration of the mechanisms of action of phytochemicals to control cancer [6]. This review identifies and discusses the various phytochemical in a number of common plants/fruits that we intake.

WHY PHYTOCHEMICALS?

Findings from various laboratory studies [7] have shown that phytochemicals have the tendency to do the following actions.

1. Acts as a supplement to boost immune system
2. Helps to arrest carcinogens forming substances that we consume.
3. Helps to decrease inflammation that stimulates cancer growth.
4. Helps to stabilize unstable molecules that can trigger cancer
5. Help in hormone regulation
6. Fight against carcinogens from attacking healthy cells
7. Prompt damaged cells to self-destruct (autophagy) before reproduction.

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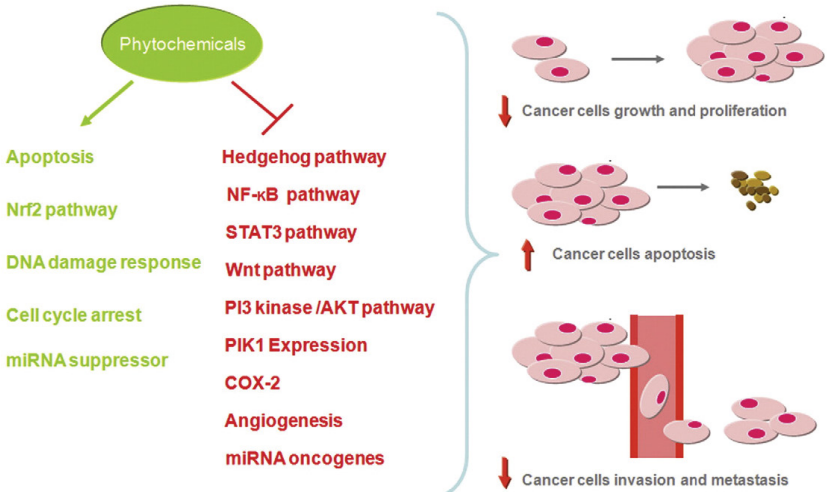

Figure 1: Various anti-cancer mechanisms of phytochemicals [6].

8. Slows down the growth rate of carcinogens.
9. Helps to put a stop to DNA damage

In addition, they significantly reduce the risk of many cancers [8]:

1. Reduced incidence of neoplasia induced by chemical carcinogens
2. Preventing nitrosation of susceptible secondary amines and amides to form highly potent carcinogenic nitrosamines and nitrosamides in our foods
3. Potent chemical nucleophiles
4. Inhibitors of kinases by reducing hyper proliferation of Epithelial cells
5. Induction of carcinogen detoxification
6. Inhibition of tumor cell proliferation
7. Antimicrobial effect, Free radical scavenging (Antioxidant effect)
8. Inhibition of DNA adduct formation
9. Induction of apoptosis and cell cycle arrest
10. Modification of carcinogen and tumor metabolism

TYPES OF PHYTOCHEMICALS

There are three major phytochemicals groups: polyphenols, terpenoids and thiols. Polyphenol group consists of flavonoids, phenolic acids and other non-flavonoid polyphenols such as tannin, curcumins, lignans. The terpenoids are classified into carotenoids and non-carotenoid terpenoids. The thiols includes the glucosinolates, allyl sulfides and non-sulphur containing indoles [9]. Antioxidant property of the phytochemicals helps to prevent cell damage from free radicals [10]. So far, several phytochemicals have been identified, and scientists have started investigating very few (Table 1) lists some of the better researched phytochemicals, their food sources and potential benefits [7].

PHYTOCHEMICAL SCREENING

Phytochemical screening are carried out for all the extracts as per the standard methods [11-14]. To detect the alkaloids, Mayer's test, Wagner's test, Dragendroff's test, and Hager's test are conducted. For the detection of carbohydrates, Molisch's test, Benedict's test, and Fehling's test are utilized. Modified Borntrager's test, Lega's test, and Keller-Kiliant test are used for detecting glycosides. Saponins are detected using Froth test and Foam test. Phytosterols are detected using Libermann Burchard's test and Salkowski's test. Ferric Chloride test is used to detect phenols, while flavonoids are detected using Alkaline Reagent test and Lead acetate test. Tannins are detected using Gelatin test and proteins and aminoacids using Xanthoproteic test and Ninhydrin test. Copper acetate test is used for detecting diterpenes.

ANTICANCER PHYTOCHEMICALS

Phytochemical studies of our previous research work on black and green grape extracts are shown in (Table 2) [15]. The extracts were prepared using both electrical pulses as well as standard methods. Here, + indicates the presence of phytochemicals, ++ indicates the presence of abundant phytochemicals, - indicates the absence of phytochemicals. The black grape extracts contained the following phytochemicals: phenol, tannin, flavonoid, saponin, anthocyanin, catechin, alkaloids, anthraquinones, carbohydrates, terpenoids, and it does not contain steroid, carotenoid. The green grape extracts contained the following phytochemicals: phenol, tannin, flavonoid, saponin, catechin, alkaloids, anthraquinones, carbohydrates, and it does not contain anthocyanin, steroid, terpenoids, carotenoid. Grape extract exhibited the biological activities such as anticancer and antioxidant activity. The antioxidant capacity of 50 µl concentration of grape extract is 78.43%. The effectiveness of the grape extract was studied against cervical cancer, using Hela Cells. Grape extract exhibited potential anticancer effect against cervical cancer cell Hela. Cytotoxicity studies revealed that, 50% inhibition concentration of grape extract is obtained as 115.05 µg/ml. Table 3 shows the phytochemical studies of our previous research work on *Vinca rosea* root extract. The ethanolic extracts of *Vinca rosea* roots indicated the presence of alkaloids, flavonoids, and terpenoids and the absence of saponin, polyphenols, steroids, and tannins [16]. Here also both electrical pulses and standard method were used to prepare the extract using ethanol. Table 4 shows the preliminary phytochemical analysis of a few selected spices [17], including *Capparis spinosa* (Caper's shrub), *Cinnamomum verum* (Cinnamon's stem), *Illicium verum* (Star anise's bark), *Allium sativum* (garlic bulbs), and *Curcuma longa* (turmeric's stem). From this study, it is revealed that *Cinnamomum verum* contains more number of biologically active constituents. The root and leaf extracts of the five plants, *Baptisia tinctoria*, *Sivapithecus indicus*, *Passiflora edulis*,

Table 1: Classification of phytochemicals with notable food rich sources and their health benefits.

Phytochemicals			Plant Source	Benefits
Polyphenol	Flavonoids	Flavonols: quercetin, kaempferol	onions, kale, leeks, broccoli, buckwheat, red grapes, tea, and apples	May inhibit inflammation and tumor growth; may aid immunity and boost production of detoxifying enzymes in the body.
		Flavones: apigenin, luteolin	celery, herbs, parsley, chamomile, rooibos tea, and capsicum pepper	
		Isoflavones: genistein, daidzein, glycitein	soya, beans, chick peas, alfalfa, and peanuts	
		Flavanones: naringenin, hesperitin	citrus fruit	
		Anthocyanidins	red grapes, blueberries, cherries, strawberries, blackberries, and raspberries	
		Flavan-3-ols tannins: catechins, epicatechin,	tea, chocolate, and grapes	
		Flavanolols: silymarin, silibinin, aromadedrin	milk thistle, and red onions	
		Dihydrochalcones: phloridzin, aspalathin	apples, and rooibos tea	
	Phenolic acids	Hydrobenzoic acids: gallic acid, ellagic acid, vanillic acid	blackberries, grape seed, pomegranate, raspberries, tea, and vanilla	May prevent cancer formation, prevent inflammation and work as antioxidants
		Hydroxycinnamic acids: ferulic acid, P-coumaric acid, caffeic acid, sinapic acid	blueberries, cinnamon, coffee, kiwi fruit, plums, and wheat bran	
	Other non-flavonoid polyphenols	Other tannins	beans, berries, cereals, cocoa, fruits, nuts, and wine	
		Curcuminoids: curcumin	turmeric	
		Stilbenes: cinnamic acid, resveratrol	blueberries, grapes, peanuts, raspberries, and wine	
		Lignans: secoisolariciresinol, enterolactone, sesamin	grains, flaxseed, and sesame seeds	
Terpenoids	Carotenoid terpenoids	Alpha, beta and gamma carotene	carrots, kale, pumpkin, and sweet potato	May inhibit cancer cell growth, work as antioxidants and improve immune response
		Zeaxanthin	corn, eggs, kale, spinach, red pepper, pumpkin, and oranges	
		Lycopene	tomatoes watermelon, pink grapefruit, guava, and papaya	
		Astaxanthin	salmon, shrimp, krill, and crab	
	Non-carotenoid terpenoids	Saponins	chickpeas, and soya beans	May protect cells from becoming cancerous, slow cancer cell growth, strengthen immune function, limit production of cancer-related hormones, fight viruses, work as antioxidants
		Limonene	the rind of citrus fruits	
		Perillyl Alcohol	caraway seeds, cherries, and mint	
		Phytosterols: natural cholesterols, siosterol, stigmasterol, campesterol	vegetable oils, cereal grains, nuts, shoots, seeds and their oils, whole grains, and legumes	
		Ursolic acid	apples, cranberries, peppermint, prunes, oregano, and thyme	
		Ginkgolide and bilobalide	Ginkgo biloba	
Thiols		Glucosinolates: isothiocyanates and dithiolthiones	cruciferous vegetables such as asparagus, broccoli, brussel, cauliflower, horseradish, mustard, radish, and sprouts	May induce detoxification of carcinogens, limit production of cancer-related hormones, block carcinogens and prevent tumor growth
		Allylic sulfides: allicin and S-allyl cysteine	garlic, leeks, and onions	
		Indoles: Indole-3-carbinol	broccoli, brussel, and sprouts	
Other phytochemicals		Betaines	beetroot	
		Chlorophylls	green leafy vegetables	
		Capsaicin	chilli	
		Piperine	black peppers	

Acacia longifolia, *Solanum trilobatum* are summarized in Table 5 [18]. *Solanum trilobatum* has indicated the presence of phytochemicals, such as alkaloids, flavonoids, glycosides, phenols, saponins, sterols, and tannins. Thus, the preliminary phytochemical screening tests helps to detect the bioactive compounds. Further steps such as purification and characterization is necessary for the development of drugs. T chloroform, methanol, and n-hexane are summarized in Table 6 [15]. The chloroform extracts exhibited the presence of few phytochemicals such as alkaloids, flavonoids, reducing sugar, saponins, tannins, and terpenoid except glycoside, anthraquinone, phlobatannin, and steroid. The methanolic extracts showed the presence of all screened phytochemicals, such as alkaloids, anthraquinone, flavonoids, glycoside, phlobatannin, reducing sugar, saponins, steroid, tannin, and saponin. n- Hexane extracts traced very few phytochemicals such as flavonoids, reducin he results of the phytochemical screening of *T. stocksianum* extracts by using solvents such as g sugar, saponins, tannins, and failed to detect alkaloids, anthraquinone, glycoside, phlobatannin and terpenoid [19]. In addition to fruits and plants, phytochemicals are also abundant in marine algae and seaweed. *Gdelidiella acerosa* (Marine red algae) showed [20] the presence of various phytochemicals. Table 7 furnishes the various phytochemicals found in this. Similarly the phytochemicals in the marine seaweed, *Sargassum wightii* is furnished in Table 8 [21]. *Sargassum wightii* were collected from the Gulf of Mannar, at the Mandapam coast, Tamil Nadu, South India. More phytochemicals are present in ethyl acetate extract of *S. wightii*. The abundance of phytochemicals in ethyl acetate, ethanol, and methanol extract is attributed by the mid-polar nature of the solvents. *S. wightii* extract prepared using non-polar solvents such as hexane, and methylene dichloride has less number of phytochemicals than the mid-polar solvent's S. wightii extract. Their extracts were treated on lung cancer cells, A549 and found to be effective. Without notable cytotoxicity, their extracts were found to be effective in targeting PI3K or its components. Earlier studies [22-24] report that they have antioxidant, anticoagulant, anticholinesterase, antimicrobial, antifertility, antifungal, and anticancer properties. A comparison with the phytochemicals in the Rwandan plants (Table 9) indicate that similar phytochemicals are present in those too [25]. This means the drug developed using these phytochemicals could be made in other countries, which means the cost could be considerably reduced and with reduced cost and side effects using these natural phytochemicals extract, it is possible to better serve the cancer patients.

Table 2: Phytochemicals in various aqueous grape fruit extracts [15].

Compound	Black grape	Green grape
Phenol	++	++
Tannin	+	++
Flavonoid	++	+
Saponin	+	+
Anthocyanin	+	-
Catechin	++	+
Alkaloids	+	+
Anthraquinones	+	+
Steroids	-	-
Carbohydrates	+	+
Terpenoids	+	-
Carotenoids	-	-

Table 3: Phytochemical screening of *Vinca rosea* root extract [16].

Compound	Tests	Color	*Vinca rosea*
Flavonoids	Ammonia solution Test	Yellowish to Brown Orange	Present
Saponin	Froth Test	Frothing	Absent
Alkaloids	Mayer's Test	Creamy white	Present
Polyphenols	Ferric chloride Test	Bluish Black	Absent
Steroids	Acetic anhydride test	Violet to blue	Absent
Terpenoids	Salkowski Test	Reddish Brown	Present
Tannins	Ferric chloride Test	Blue or Green	Absent

Table 4: Phytochemicals in a few selected spices [17].

Compound	Capparis spinosa (Caper's shrub)	Cinnamomum verum (Cinnamon's stem)	Illicium verum (Star anise's bark)	Garlic Cloves (Garlic bulbs)	Curcuma longa (turmeric's stem)
Carbohydrate	+	+	+	+	+
Proteins	+	+	++	+	+
Glycosides	+	+	-	++	-
Steroids	+	++	-	-	++
Alkaloids	++	++	-	++	-
Flavanoids	++	++	+	+	-
Saponins	-	+	-	-	+
Anthraquinones	-	++	+	-	-
Tannins	++	++	-	-	-
Terpenoids	+	+	+	+	-
Anthocyanins	-	-	-	+	+
Coumarins	-	+	-	-	-
Emodins	-	-	+	-	-

Table 5: Phytochemicals in some selected plants [18].

Compound	Baptisia tinctoria	Sivapithecus indicus	Passiflora edulis	Acacia longifolia	Solanum trilobatum
Alkaloids	-	-	-	-	+
Cardiac glycoside	+	+	+	+	+
Flavonoid	+	+	+	-	+
Terpenoid	+	-	+	-	+
Phenol	+	+	+	+	+
Steroids	+	+	+	+	+
Saponin	+	+	+	+	+
Tannin	+	+	+	+	+

Table 6: Phytochemical screening of *Teucrium stocksianum* using different solvents [19].

Phytochemicals	Chloroform	Methanol	n-Hexane
Alkaloids	+	+	-
Anthraquinone	-	+	-
Flavonoids	+	+	+
Glycoside	-	+	-
Phlobatannin	-	+	-
Reducing sugar	+	+	+
Saponins	+	+	+
Steroid	-	+	-
Tannins	+	+	+
Terpenoids	+	+	-

Table 7: Phytochemicals in *Gelidiella acerosa* [20].

Phytochemical	Hexane	Methylene dichloride	Ethyl Acetate	Ethanol	Methanol	Water
Alkaloids	+++	++	++	-	-	-
Carbohydrate	-	-	+	+++	+++	+++
Coumarins	-	+	+++	++	++	+
Flavonoids	+	+	+++	+++	++	++
Glycoside	+++	+++	+++	+++	+++	+
Oils and Fats	++	++	+++	++	++	-
Phytosterol	-	+++	+++	+++	+++	-
Protein	-	+	+	+++	+++	++
Resins	-	-	-	++	++	-
Saponins	-	-	-	-	-	-
Tannins	-	+	+++	++	+++	-
Terpenoids	-	-	+++	+++	+++	-

Table 8: Phytochemicals in *Sargassum wightii* [21].

Phytochemical	Hexane	DCM	Ethyl Acetate	Ethanol	Methanol
Carbohydrates	-	-	++	+++	+++
Fats and Oils	-	-	++	+++	+++
Flavonoids	++	++	+++	++	+++
Glycosides	+	+	+++	+++	+++
Phytosterols	++	++	+++	++	+
Protein	-	-	++	+	+
Resins	-	-	+++	++	+
Saponins	-	-	-	-	-
Tannins	++	++	+++	++	+
Terpenoids	-	-	+++	++	+++

Table 9: Phytochemicals in Rwandan plants [25].

Phytochemical	Vernonia amygalina	Lantana camara	Veronia aemulans	Markhamia lutea
Alkaloids	+	+	+	+
Glucosides	+	+	+	+
Carbohydrate	+	+	+	+
Flavonoids	+	+	+	+
Phenols	+	+	+	-
Saponins	+	+	+	+
Steroids	+	-	+	+
Phlobatannins	-	-	-	-
Tannins	+	+	+	+
Terpenoids	+	-	+	-

CONCLUSION

Phytochemicals from grapes, *Vinca rosea*, spices, marine red algae and similar other resources could be effectively used as cost effective alternative to conventional expensive medicines used for anticancer treatment. They are gentle on our bodies and have no or less side effects. Either as the pure compounds or as standardized extracts, they provide unlimited opportunities for new drug leads because of the unmatched availability of chemical diversity. The bioactivity of natural products is associated with the effects of various phytochemicals, such as tannins, terpenoids, cardiac glycosides, saponins, flavonoids among others. The extracts can be prepared using electrical pulses with over 10% increased volume. Also, they could be uploaded into the tumor using electrical pulses (electrochemotherapy [26,27]), providing a new treatment modality that could be transferable to clinical practice.

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