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Review article

Potential phytochemicals in the prevention and treatment of esophagus cancer: A green therapeutic approach

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ABSTRACT

Globally, esophagus cancer (EC) is one of the most frequently reported malignancies and leading cause of deaths. Currently, different treatment methods are available like chemotherapy, radiation therapy, surgery or their combination. These treatment strategies are not enough and are often associated with adverse side effects. The alternate treatment option like phytochemicals have come up with ease of bioavailability and cost-effectiveness. Due to general acceptance, lower side effects, safety and pleiotropic effect, phytochemicals can be used as an adjuvant treatment for alleviating side effects associated with chemotherapy and radiotherapy. Phytochemicals perform multiple functions; release cytochrome-c, loss mitochondrial membrane potential, down-regulate expression of anti-apoptotic proteins, up-regulate pro-apoptotic proteins, activate caspases, p53, inhibit Akt/mTOR signaling pathway, phosphorylate NF-κB, STAT3 and PI3K. The knowledge compiled here encompasses anti-EC phytochemicals, their occurrence, bioavailability therapeutic effects and mechanism of action by targeting several genes and signaling pathways. Overall, the clinical data compiled on phytochemicals against EC is not sufficient and need future research to provide additional insights for developing potential anticancer drugs in pharma industries.

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Esophagus cancer: a global concern

Esophagus cancer (EC) is a complex and heterogeneous disease and is categorized seventh in terms of incidence (572,000 new cases) and sixth in mortality overall (509,000 deaths), indicates that EC will account for an estimated 1 in 20 cancer deaths in 2018 and claims more than 400,000 lives around the world each year [1–3]. It has been estimated that in the United States alone there will be ~17,290 new cases and 15,850 deaths in 2018 [4]. EC is extremely aggressive disease and prognosis is often very poor [5,6]. The incidence rate of EC varies as 323,000 males and 133,000 females cases [2.4:1] in 2012 where, the incidence among males and females varied as much as 20 times in different regions. The etiology of EC differs from country to country and from individual to individual and as a big challenge for the scientific community to develop its chemoprevention and chemotherapeutics [7,8]. EC is generally malignant with around 0.5% of them are benign and majority of the cases (80%) are reported from low-income countries.

Based on histology EC is usually categorized into 2 subtypes, esophagus squamous cell carcinoma (ESCC) and esophagus adenocarcinoma (EADC) [9] having wide range of distribution in South-Eastern, Central Asia, Northern and Western America and Oceania [9]. EC is the leading cause of mortality in Kenyan men, whereas, Malawi exhibits the highest incidence rates globally in both male and female. Incidence rates in Eastern Africa rank third by region in men with the highest rates in Eastern Asia, where rates in Mongolia and China are in the top 5 worldwide [2]. ESCC and EADC can be distinguished on the basis of etiology, epidemiology and pathogenesis [10].

EADC represents the majority of cases in high-income countries with risk factors include age, gastroesophageal reflux disease (GERD), smoking, obesity and diet deficient of fruits/vegetables. However, for ESCC smoking, alcohol, poor oral hygiene, intake of causative agents and nutrient deficiency are the main risk factors [5,11]. ESCC cases are generally reported from lower income countries while that of EADC are found in developed countries [10]. The global incidence rate of ESCC is higher than EADC [12]. The rate of incidence of ESCC is higher in African Americans than in European Americans is on decline in both as compared with to EADC. Furthermore, the incidence rate of EC is different in both male and female in America (2–3 folds higher in men than women) [13]. Similarly, the incidence rate of EC is higher in men than women in Chinese which is 3–5:1 [14]. An Indian research work investigated 3 times more incidence and death rate in men than women [15]. In Gezira, Sudan male to female ratio is 1:3.3 [16]. The highest rate of incidence of EC is found in Chinese, Ethiopians, UK, Iceland and Japanese [7]. Different population have different carcinogenic agents. In North America and Western Europe tobacco and alcohol, in Hong Kong pickled vegetables, in Taiwan and India tobacco and betel quid, in Iran opium are reported to be the main factors for causing EC [13]. Despite the advancement in therapeutic and diagnostic procedures many patients have poor prognosis of EC when suffering from advanced and metastatic diseases [14]. The 5-years survival rate even after advanced radical esophagectomy is lower than 20% in Chinese and above 15% in the US.

Although, there are many different approaches for the treatment of EC such as chemotherapy, radiation therapy, surgery or their combinations. However, these treatments are not sufficient due to lack of effective therapy, adverse side effects, chemoresistance and disease recurrence. These complications compel researchers to develop alternative and safer therapeutic strategy. Therefore, phytochemicals are of major interest due to high bioavailability, safety, high specificity, efficacy and fewer side effects.

Current esophagus cancer treatment *via* phytochemicals: a novel approach

Phytochemicals are bioactive compounds largely distributed in plants with the potential to reduce the risk of various diseases. There are more than 50,000 different phytochemicals present in plants. Several potential phytochemicals have been reported for the treatment of EC such as icariin, luteolin, curcumin, gallic acid, oridonin, sinomenine, quercetin, apigenin, matrine, berberine, artesunate and have shown promising results by enhancing cancer therapeutics through different mechanisms [Fig. 1]. In this review article and within this contribution, we have discussed the preventive potentials, therapeutic effects and mechanism of action of these phytocompounds for the treatment and management of EC [Table 1].

Scientists have investigated that high consumption of fruits/vegetables have significantly reduced the occurrence of EADC and ESCC as they are reservoirs for potential bioactive compounds [17–19]. A wide range of meta-analyses and case studies have reported that high consumption of fruits/vegetables have shown inverse relationship with EC. The research studies conducted by Yang et al. [13], Sardana et al. [20], Kubo et al. [21] and Castellsague et al. [22] have confirmed their protective nature. Furthermore, a meta-analysis done in Japan has shown that fruits possess more protective nature than that of vegetables. Lower consumption of vegetables, fruits, deficiency of riboflavin, vitamins A and C may increases EC risk [23].

Different types of beans, green vegetables (cabbage, cauliflower, carrot, onion, garlic, tomato, celery, potato, brinjal) are rich source of anticancer agents which provide strong protection against cancer. Similarly, phytochemicals are also widely distributed in grapes, strawberries, melons, citrus fruits, apples, plums, pineapple. The anticancer potential of vegetables and fruits is not just because of few vitamins, minerals, but also because of a group of some other therapeutic agents such as vitamin C, E, isoflavones, beta carotene, selenium, folic acid, dithiolthiones, indole-32-carbinol, isothiocyanate, inositol, phytosterols, lycopene, dlimonene, protease inhibitors, saponins, and lutein (Table 2). Literature from different research papers was thoroughly reviewed from ISI web of knowledge, google scholar and many other sites (Fig. 2). This review article encompasses knowledge regarding different phytochemicals involved in EC chemoprevention by putting in view the recently recognized molecular mechanisms and soft targets, which may serve useful in future dugs development.

Sinomenine (SIN)

SIN is a potential phytochemical isolated from *Sinomenium acutum* and is used for the treatment of different diseases with

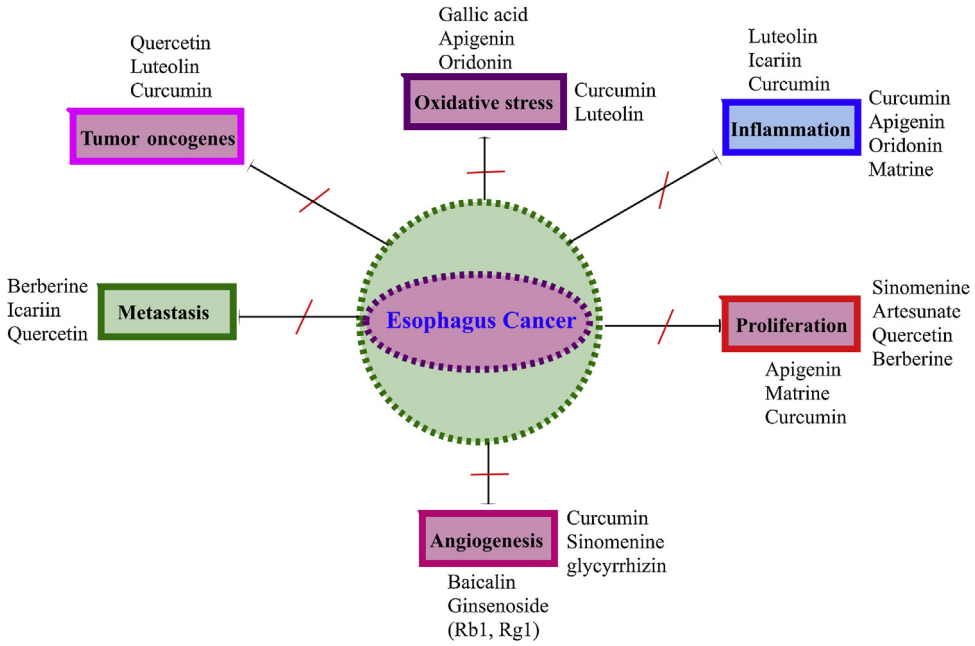

Fig. 1. Different mechanisms of phytochemicals in the chemoprevention and chemotherapeutics of esophagus cancer.

low side effects. Furthermore, SIN possess some other pharmacological potentials. SIN has the potential to arrest cell cycle at G1 phase, induces caspase mediated cell death and inhibit angiogenesis [24,25]. It has been researched that SIN can induce apoptosis and inhibit cancer cell proliferation in different cancer [26]. Wang et al. [27] in his research study determine the potential of SIN combined with 5-fluorouracil on EC and observed that combinatorial effect of 5-FU and SIN on the apoptosis and proliferation of human EC was found higher than that of their individual effect. In addition, SIN can result in disruption of mitochondrial membrane potential which eventually leads to caspase-mediated apoptosis. These potentials may suggest SIN, a lead candidate for possible anticancer drug development in pharma industries.

Table 1
Potential phytocompounds obtained from medicinal plants and their anticancer potential against esophagus cancer.

Plant name	Family	Potential agent	Chemical Category	Study type	Molecular targets	Literature cited
Chrysanthemum morifolium	Asteraceae	Luteolin	Flavonoid	*In vitro*	Induced cell cycle arrest and apoptosis though mitochondrial pathway	[58]
Rabdosia rubescens	Lamiaceae	Oridonin	Terpenoid	*In vitro*	Inhibit tyrosine kinase activity, regulate the expression of p53 and BCL-2 family	[30,54]
Curcuma longa	Zingiberaceae	Curcumin	Hydrocarbon	*In vitro*	Induces cell cycle arrest and apoptosis, inhibit NF-κB and Notch signaling pathway	[70,71]
Dendrobium	Orchidaceae	Quercetin	Flavonoid	*In vitro*	Inhibit the expression of oncogenes and related enzymes, induces cancer cell apoptosis and differentiation	[34,35]
Perilla frutescens	Lamiaceae	Apigenin	Flavonoid	*In vitro*	Disrupt mitochondrial membrane potential, induces apoptosis and arrest cell cycle	[3,45]
Ligustrum lucidum, Sambucus chinensis	Adoxaceae,	Ursolic acid	Treiterpene	*In vitro, in vivo*	Effect BCL-2 gene family protein expression, inhibit the functions of COX-2 and PGE2,	[81]
Perilla frutescens	Lamiaceae	Luteolin	Flavonoid	*In vitro*	Induced cell cycle arrest and apoptosis though mitochondrial pathway	[45]
Sophora flaavescens	Leguminosae	Matrine	Alkaloid	*In vitro, in vivo*	Regulate the level of apoptosis related proteins, arrest cell cycle	[55]
Epimedium brevicornum	Berberidaceae	Icariin	Flavonol glucosides	*In vitro*	Inhibit the PI3 K/AKT, STAT3 signaling pathway, regulate the production of ROS and alter MMP	[64,68]
Scutellaria barbata	Lamiaceae	Luteolin	Flavonoid	*In vitro*	Induced cell cycle arrest and apoptosis though mitochondrial pathway	[46]
Coptidis Rhizoma, Coptis japonica	Ranunculaceae	Berberine	Alkaloid	*In vitro*	Regulate multiple pathways: Akt, mTOR, AMPK, induces apoptosis and promotes cell cycle	[38,44]
Sinomenium acutum	*Menispermaceae*	Sinomenine	Alkaloid	*In vitro*	Induce caspase mediated apoptosis, inhibit angiogenesis, arrest cell cycle	[24,25]
Panax Ginseng.	Araliaceae	Ginsenoside Rh2	Ginsenoside	*In vitro, in vivo*	Effect cell cycle protein expression, induces cell differentiation tending to normal	[80]
Scutellaria barbata	Lamiaceae	Apigenin	Flavonoid	*In vitro*	Induces cell cycle arrest, result in apoptosis, disrupt mitochondrial membrane potential	[3,46]
Artemisia annua	Asteraceae	Artesunate	Ester	*In vitro*	Effect signal transduction and DNA synthesis, disrupt cytoskeleton, inhibit cell migration and invasion	[29,30]
Phaleria macrocarpa	Thymelaeaceae	Gallic acid	Phenylmethyl ester	*In vitro*	Modulate the expression of proteins, caspase-cascade activity, survival Akt/mTOR signaling pathway	[32]

Table 2
Dietary sources of phytochemicals and their mechanism of action in the treatment of esophagus cancer.

Food source	Potential agents	Mechanism of action on EC	Literature cited
Oil of citrus fruits peel	Terpenoids	Inhibit cancer cells metastasis and proliferation	[108]
Leeks, onion, garlic,	Allium compounds	Act on cytochrome P450 and reduces the pro-carcinogens	[86]
Wheat, oats, rye, soya beans, cereals	Protease inhibitors	Reduces the incidence of EADC	[100]
Fruits and vegetables	Flavonoids	Having anti0xidant, anti-inflammatory, anticancer potential	[109]
Nuts, beans, pea nuts, soya beans,	Phytic acid	Induces apoptosis, inhibit proliferation, regulate cell cycle arrest	[101]
Cruciferous vegetables	Isothiocyanates	Reduces cancer cell growth and arrest cell cycle, decrease cancer development by inhibiting different signaling pathways *e.g.* NF-κB	[89]
Fruits, vegetables	Phenolic compounds	Induces apoptosis, inhibit proliferation, angiogenesis	[10]
Soya beans, colocasia	Saponins	Induces apoptosis, arrest cell cycle in EC, inhibit COX-2 signaling pathway	[110]
Soya beans, berries, cereals, pulses	Phytoestrogens	Prevent cancer cells progression, suppress tumor growth	[100]
Cereals, grains, fruits, vegetables	Fiber (macronutrients)	Reduces cancer cell growth, proliferation, induces apoptosis, down-regulate tumor necrosis factor α, absorb carcinogens in GIT	[111,112]
Vegetables	Plant sterols	β sitosterol decreases the risk of ESCC	[113]
Cruciferous vegetables	Dithiolthiones/ glucosinolates	Induces cell cycle arrest, inhibit NF-κB, inhibit enzymes responsible for pro-carcinogens	[87]
Orange, fruits and dark green leafy vegetables	Carotenoids	Reduces the oxidative stress by chronic acid reflux	[85,114]

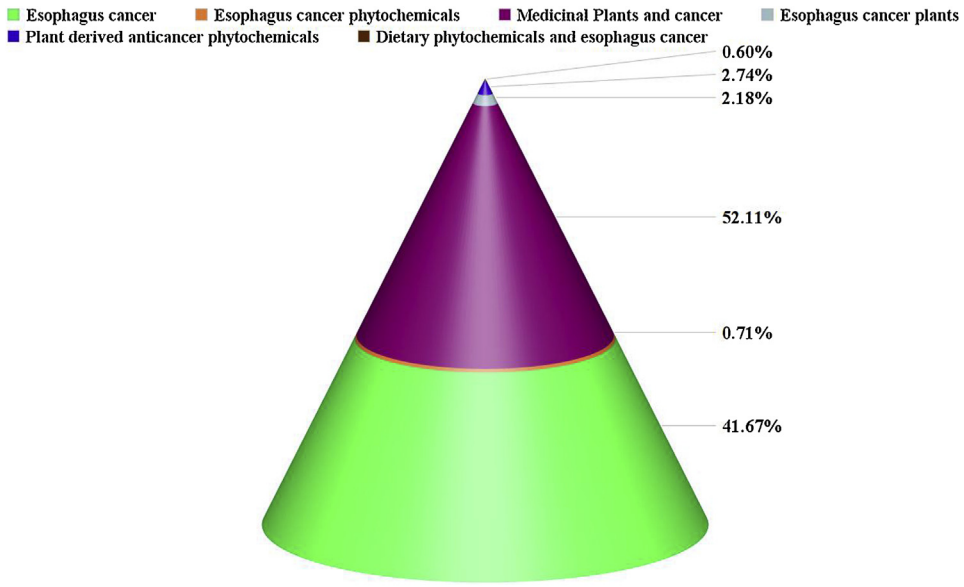

Fig. 2. Research work published on phytochemicals used for the treatment of esophagus cancer. Different keywords were searched related to phytochemicals, esophagus cancer and their percentage % is given.

Artesunate

Artesunate, a semisynthetic derivative of artemisinin (*Artemisia annua*) is a strong bioactive compound used as an anti-malarial drug in pharmaceutical industry and possess strong anticancer potentials against various types of tumors [28,29]. Artesunate has significantly suppressed cancer cell proliferation, migration and arrest cell cycle at G0/G1 phase in KYSE-150 cell line [29]. The artesunate can mainly destroy the cytoskeleton structure of cancer cells. The cytoskeleton mainly comprised of microtubules, microfilaments and intermediate flaments which determine morphology and biochemical characteristics of cell under different physiochemical condition. It alteration can effect chromosomal stability and cell proliferation [30]. By damaging cytoskeletal network of cancer cells, artesunate can regulate cell signaling, DNA synthesis and cell migration [29]. The destroyed cytoskeletal network caused by artesunate can enhance apoptotic processes, thereby showing promising anticancer effect. In nutshell, artesunate can be a novel and potential candidate for anticancer drug development in pharma industry.

Gallic acid (GA)

GA is a promising phytochemical with anti-oxidant potential and is widely distributed in grapes, bananas and strawberries [31]. GA extracted from *Phaleria macrocarpa* has shown strong anticancer potential in the treatment of cancer. It different parts (fruits, seeds) have been widely used for the treatment of various diseases [32]. GA can perform function by scavenging free radical and induces apoptosis in different types of tumors. GA play significant role in the prevention of EC without harming normal cells [33]. GA can be used to prevent and treat EC through different mechanisms involving the regulation of survival Akt/mTOR signaling cascade, modulate caspase cascade activity, regulate protein expression and ultimately results in cell cycle arrest [32]. Furthermore, GA can perform anticancer function by increasing the

expression of pro-apoptotic protein (Bax), decreases the expression of anti-apoptotic proteins (Bcl-2, XIAP), induces caspase-cascade and down-regulate Akt/mTOR signaling pathway [32]. These different studies suggest GA as a strong phytocompound and can be used in pharmaceutical industries for the treatment of different types of cancer.

Quercetin

Quercetin is also a strong phytochemical isolated from different fruits and vegetables and has shown strong anticancer potential by inducing apoptosis, arrest cell cycle, thereby inhibiting the expression of oncogenes [34]. Quercetin has also shown strong anticancer potential by regulating activity of topoisomerase II and protein kinases [35], regulate level of B-cells chronic lymphocytic leukamia/lymphoma 2 (Bcl-2), reorganizes DNA and arrest cell cycle [35,36]. In this way, quercetin inhibit EC cells proliferation and induces caspase mediated cell death. Quercetin alone has shown mild anticancer potential, but has shown strong cytotoxic and apoptotic potential when combined with lower concentration of 5FU. These research studies have confirmed quercetin is a potential candidate to enhance cell sensitivity to 5-FU by inhibiting NF-κB signaling pathway [37]. As quercetin is a strong phytochemical thus can be utilized in pharma-industries for potential drug development.

Berberine

Berberine is a natural alkaloid widely distributed in *Coptidis rhizoma*, *Coptidis chinensis*, *Coptidis japonica* and *Hydrastis canadensis* [38]. These plants are used for the treatment of different diseases like gastrointestinal disorders (*C. rhizoma*) [39]. Berberine is also a very important constituent of medicinal herb Oren-to with having strong anticancer potential by inhibiting cancer cell growth and progression [40]. Moreover, *C. rhizoma* has alleviated stomach discomfort and has strong cancer chemopreventive and chemotherapeutic effect [41]. Berberine isolated from *C. rhizoma* has potential anticancer effect on different cancer cell lines without harming the healthy cells [40,42]. Berberine modulate tumor development *via* regulating different signaling cascades, induces apoptosis, inhibit proliferation and arrest cell cycle [38,43]. In case of human EC, berberine can inhibit cancer cells invasion and metastasis by targeting different chemokine receptor [42]. Moreover, berberine possess strong anti-proliferative potential by arresting cell cycle at G2/M, thereby interfering with Akt/mTOR signaling pathway [44]. The berberine isolated from *C. rhizoma* can also be used as a drug in stomach related disorders. These different research findings strongly recommend berberine as a potential candidate in pharma industries for drug development.

Apigenin

Apigenin is also a widely distributed natural phytochemical in different fruits, vegetables and other medicinal plants such as *Perilla frutescens* [45], *Scutellaria barbata* [46]. It also exhibit different pharmacological potential like anti-oxidant, anti-inflammatory and anticancer. Apigenin is used to treat cancer cells by preventing cancer cells growth, induces apoptosis, arrest cell cycle and disrupt membrane potential [3,47]. Furthermore, apigenin causes cell membrane toxicity which results in damaging membrane ultrastructure and enhance membrane permeability, result in cell apoptosis which is beneficial for the anticancer potential of apigenin [3]. Different research studies have investigated the potentials of apigenin on EC by inhibiting the growth and proliferation of human EC cells (KYSE150, EC9706) and potentially destroy cell membrane structure which function as an anticancer target [3]. Additionally, cancerous cells are more specific to anticancer effect of apigenin than normal healthy cells. This specificity suggest apigenin a potential candidate for targeting specific type of cancer. These research findings strongly recommend apigenin for pharma industry to develop anticancer therapeutics [3].

Oridonin

Oridonin is a strong phytochemical isolated from *Rabdosia rubescens* used for the treatment of EC [48]. Oridonin may also perform different other biological functions such as anti-microbial, anti-oxidant anti-inflammatory and anticancer [3,49]. It has shown potential anticancer effects on different types of malignant tumors [49,50] and have been used in the clinical treatment of solid tumor especially EC [51]. The oridonin perform its anti-tumor function by modulating Bcl-2 protein and caspase enzymes [52]. Furthermore, it also increases the expression of Bcl-2/Bax proteins, decreases Bcl-x(L) and Mcl-1 proteins. In addition, oridonin is used to treat EC cells by activating caspases, induces apoptosis through mitochondrial dependent pathway [53]. Moreover, it also has the potential to treat EC by inhibiting the activity of DNA polymerase and tyrosine kinase [54]. EGFR is a receptor on the cell surface responsible for specific interactions with ligands to activate downstream signaling proteins and pathways [54]. Thus, oridonin down-regulate the expression of EGFR and interfere the interaction between EGFR and specific ligands thus playing anticancer potential [54]. There are also some limitations associated with oridonin; poor water solubility and high toxicity which restrict their extensive biological applications [54]. Scientists are trying to solve these problems by developing synthetic analogs. Research studies have evaluated oridonin is a powerful candidate and can be used in pharma industries for anticancer drug development.

Matrine

Matrine is a novel alkaloid obtained from *Sophora flavescens* and has shown potential chemotherapeutic properties. Matrine has strong anti-inflammatory, anti-fibrosis and anti-virus potentials and can be used for the treatment and management of liver cirrhosis and viral hepatitis [55]. In several other research studies, matrine has shown strong anticancer potential in a wide range of cancer cells, where it can potentially inhibit EC cells proliferation and migration thus induces apoptosis [56,57]. Further research studies investigated that matrine could significantly decreases EC cells viability by arresting cell cycle and inducing apoptosis to regulate apoptosis associated proteins (p21, BID, p53) [56]. The essential member of BCL-2 family, BID perform its function by repairing DNA damage [56]. Moreover, matrine also modulate BID level, decreases the expression of BCL-2/BID and up-regulate caspase-9, eventually result apoptosis in EC cells [56]. Research studies have confirmed that matrine has low toxicity and can be used as a strong phytocompound in pharma industries for the development of anticancer drugs.

Luteolin

Luteolin is also a potential flavonoid isolated from *S. barbata* [55] and *Chrysanthemum morifolium* [58]. Luteolin possess several other biological functions such as antioxidant, anti-inflammatory and regulate immune system [59]. It has shown strong anticancer potential against different human cancers by arresting cell cycle, induces apoptosis, inhibit invasion, migration and has potential to increase the effect of chemotherapeutic drugs [46,60,61]. Different other research studies have demonstrated the effect of luteolin on EC and found that luteolin can act as a strong anti-proliferative

agent by effecting EC cells and arrest cell cycle [62]. Moreover, luteolin induces apoptosis in EC cells by mitochondrial pathway [63]. Luteolin could also increase expression level of caspase-3 accompanied with up-regulation of cytochrome-C (CYT-C) and PARP cleavage which eventually leads to mitochondrial apoptosis pathway [60]. These research studies demonstrate luteolin is a powerful candidate for the treatment of EC and strongly recommend it for developing anticancer drugs.

Icariin

Icariin is a natural phytocompound isolated from *Epimedium brevicornum Maxim* which is used for the treatment of kidney [64]. Icariin perform different pharmacological functions such as anti-inflammatory, neuro-protective, anticonvulsant and anticancer [65,66]. Icariin also perform anticancer potential on different cancer cells (liver cancer, gallbladder and EC cancer) [67,68]. Different researchers have investigated that icariin could potentially induced apoptosis in EC by regulating ROS production and alter mitochondrial membrane potential (MMP). Icariin could treat EC cells by accumulating ROS, thereby resulting in reducing MMP level. Furthermore, icariin regulate the activities of kinases, arrest cell cycle at G2/M phase and eventually result in inhibiting EC cells invasion, migration and metastasis. Different research findings demonstrate icariin as a potential candidate for pharma industries to develop different cancer therapeutic drugs [68].

Curcumin

Curcumin is a natural phytochemical isolated from rhizome of *Curcumin longa*. Different research studies have demonstrated that curcumin exhibit different therapeutic activities such as anti-inflammatory, antiviral, anti-oxidant and anticancer [69]. Recently, the anticancer potential of curcumin has attracted significant attention by inhibiting cancer cell angiogenesis, proliferation, DNA topoisomerase II and induces apoptosis [70–72]. Different research studies have also confirmed the anti-cancer potential of curcumin on EC cells [73,74] by activating caspase-3 [70], regulate Bcl-2/Bax and increases expression of notch signaling pathway, which has an implication in apoptosis and proliferation thus playing important role in tumorigenesis of EC [75,76]. The expression level of notch signaling pathway can be significantly decreased in EC, so it can be considered as a soft target for EC treatment [77]. Furthermore, caspase enzymes (caspase-3 and caspase-7) also play potential role in carcinogenesis and apoptosis. The caspase-3 activation modulate downstream signaling pathways and results in the apoptosis of cancer cells. As curcumin influence multiple signaling pathways, exhibit strong anticancer potential on EC, involve in progression of autophagy [70,73,78,79]. With having these versatile properties, curcumin can be used as a promising candidate for the treatment and management of different types of cancers.

In spite of the above mentioned phytocompounds there are some other phytochemicals having anticancer potential against esophagus cancer. These compounds include resveratrol, lutein, ginsenoside Rh2 (GS-Rh2), ursolic acid. Resveratrol has the potential to modulate the expression of proteins that effect the cell cycle arrest, DNA synthesis [80]. Ursolic acid is another widely distributed anticancer agent in ligustrum, forsythia and hawthorn, lucidum and *Sambucus chinensis* [81]. Ursolic acid has induced apoptosis in EC cells by modulating the expression of BCL-2. GS-Rh2 is phytochemical having the potential to arrest Eca-109 cells at G0/G1 phase, induces apoptosis and regulate cell cycle related proteins expression [82]. Medicinal plants are generally used in mixture form. Oren-to (a mixture of seven different constituent) possess strong anticancer potential against EC cells *in vitro* studies [40]. Sho-saiko-to is another mixture of glycyrrhizin, baicalin, ginsenoside Rb1 and Rg1 ingredients and have shown potential anticancer results against different cancer cell lines (liver cancer, cholangiocarcinoma) by inducing apoptosis and arrest cell cycle [83].

Synergistic effects of phytochemicals and EC prevention

At present, a wide range of therapies are available for the treatment of EC such as chemotherapy, radiation therapy, surgery and their combinations [84]. EC is having extremely poor prognosis and recent chemotherapy often have limited success rate and fatal side effects. Cisplatin and 5-fluorouracil (5-FU) are anticancer drugs used for the treatment of EC and have shown significant effects. For advanced type of EC patients, cisplatin and 5-FU regimen (CF) as well as docetaxel, cisplatin and 5-FU (DCF) are the standard chemotherapeutic agents for cancer [85,86]. EC easily develop resistance against different types of anticancer drugs which finally result in the failure of treatment and cause further toxicity [8,87]. Thus, many researchers have focused on the molecular mechanism of chemotherapy resistance to come up with more potential strategies [8,88].

These natural agents obtained from medicinal plants, fruits and vegetables have shown synergistic effects with potentials to increase therapeutic effects of radiotherapy, chemotherapy or their combination [89–93]. Different phytochemicals perform multiple functions such as scavenging free radicals and ROS, protect cells from oxidative damage to proteins, DNA and lipids. Furthermore, phytochemicals possess anti-inflammatory potentials by blocking cytokines, modulate multiple cell signaling cascades by inhibiting cancer cells angiogenesis and proliferation [90,94–96].

It has been investigated that quercetin enhanced the potential of 5-FU by suppressing NF-κB signaling cascade [8]. The ECC cell exposed to both quercetin and 5-FU significantly enhanced the apoptosis rate compared with 5-FU alone [8], which may result in decreased expression of NF-κB (pIkBα) triggered by exposure to 5-FU alone. These results demonstrate that co-treatment with both quercetin and 5-FU has significantly enhanced their therapeutic potential and may be the best choice for EC treatment [8].

Moreover, the co-treatment of ursolic acid with 5-FU, cisplatin and irinotecan has shown growth inhibition and cytotoxic effect on EC cell lines than 5-FU, irinotecan and cisplatin alone [97]. SIN has the ability to enhance the potential of 5-FU. The combinatorial effect of SIN along with 5-FU has potentially induced apoptosis and arrest cell cycle in human EC than the SIN and 5-FU alone [98]. Their co-treatment not only enhanced therapeutic potential but also decreased the side effects that were reported alone [98]. Furthermore, curcumin has sensitized the treatment of esophageal adenocarcinoma along with 5-FU and cisplatin [99].

Similar to chemotherapy, radiotherapy is also used for the treatment and management of EC. There are also some adverse effects associated with radiotherapy like cancer-cells resistance to radiotherapy and poor clinical outcomes. The scientific community is working hard to combat these issues. During the course of radiation therapy, oxygen release free radicals thereby causing DNA damage and kill cancer cells [100]. Different research studies have determined that radiation resistance and poor clinical results may be associated with tumor cells hypoxia [101]. So, berberine has the potential to enhance the radiosensitivity of ESCC by inhibiting the expression level of HIF-1α and RAD51 [17,100]. Furthermore, Yang et al. [13] and Liu et al. [39] has investigated that berberine can potentially inhibit the expression of HIF-1α induced by hypoxia and RAD51 thereby, enhancing the radio-sensitizing nature of hypoxic cells, thus promoting cancer cell therapeutics.

Esophagus cancer prevention and Socioeconomic status

EC is an extremely aggressive disease and therefore, its early prevention and treatment is of great importance. Approximately 30–40% of EC cases can be prevented by simple changes in life style and dietary patterns of people. A wide range of research studies performed in different parts of the world found that socioeconomic status was positively related with EC risk [102,103]. The incidence rate of EADC was higher in countries having high human development index [HDI] while that of ESCC was highly dominant in countries with low HDI [10,17]. Furthermore, Bathija et al. [8] in his research study found that ~80% of EC cases were males between 41–60 years of age, out of which 68% cases were reported in individuals with lower socioeconomic status and ~60% were reported in individuals who were illiterate and unaware of the significance of the protective effects of fruits, vegetables. Moreover, the same results were also reported in the research work conducted by Dar et al. [104].

Conclusion

The current treatment options available for cancer include chemotherapy, radiotherapy, surgery and their combination, but these treatment methods are often associated with some side effects which limit their usage in cancer therapeutics. Therefore, scientific community is working hard to find natural agents as an alternative treatment method with having low toxicity, high specificity, and cost-effectiveness. Different *in vitro* and *in vivo* research studies have confirmed that natural agents isolated from medicinal plants, fruits and vegetables have shown inverse relationship with EC. This review article has critically investigated the anticancer potentials of phytochemicals that regulate expression of different proteins, enzymes and signaling pathways (NF-κB, Bcl-2, mTOR, AMPK, p53, COX-2, PI3K/AKT, STAT3), inhibit angiogenesis, proliferation, metastasis, arrest cell cycle, induces apoptosis, down-regulate anti-apoptotic proteins and up-regulate pro-apoptotic proteins. In nutshell, phytochemicals is a promising therapeutic strategy and need future research to discover more and more anticancer agents.

Prospects and future perspectives

Medicinal plants, fruits and vegetables are potentially important. The importance of these can be determined from the statistical report of World Health Organization which estimates that ~80% of the world population fulfill their healthcare requirements from these medicinal plants [90,105]. There has been a substantial increase in the utilization of medicinal plants products including strong medicinal drugs and proved to have potential therapeutic effects with reduced/no side effects. On the other hand, therapeutic failure, toxicity and negative effects have been observed in many *in vitro* and *in vivo* studies as pharmacological methods of herbal preparations are not well investigated. The most significant concern of scientific community is to identify and optimize the exact method of preparation of plant extract, to identify the bioactive ingredients and their routes of administration [106]. Through this strategy, screening, characterization and identification of undiscovered bioactive compounds in conventional medicine can be studied. The traditional Chinese medicinal knowledge of plants will be the key area of research in the future.

Furthermore, medicinal plants cultivated in diverse regions of the world are considered to be different in phytochemical and pharmacological potential against various diseases. As for example, the medicinal plants of genus *Ziziphus* cultivated in Pakistan will have different phytochemistry compare to those present in other parts of the world. Scientific community is working hard on medicinal plants, bringing new therapeutic approaches to minimize toxicities, enhance their therapeutic potentials by developing strong derivatives/analogs [105,107].

Conflict of interest

The authors declare that they have no conflict of interest

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