FLAVONOID APPLICATION IN TREATMENT OF ORAL CANCER-A REVIEW

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ABSTRACT

A wide range of organic compounds that are naturally occurring called flavonoids are primarily found in a large variety of plants. Some of the sources include tea, wine, fruits, grains, nuts and vegetables. There are a number of studies that have proven that a strong association exists between intake of dietary flavonoid and its effects on mortality in the long run. Flavonoids at non-toxic concentrations are known to demonstrate a wide range of therapeutic biological activities in organisms. The contribution of flavonoids in prevention of cancer is an area of great interest in current research. A variety of studies, including in vitro experiments and human trials and even epidemiological investigations, provide compelling evidence which imply that flavonoids' effects on cancer in terms of chemoprevention and chemotherapy is significant. As the current treatment methods possess a number of drawbacks, the anticancer potential demonstrated by flavonoids makes them a reliable alternative. Various studies have focussed on flavonoids' anti-cancer potential and its possible application in the treatment of cancer as a chemopreventive agent. This article summarizes the effects of flavonoids in relation to its anticancer potential and its clinical application in treatment of oral cancer.

KEYWORDS: Anti-cancer; chemoprevention; flavonoids; oral cancer

INTRODUCTION

Cancer Disease is one of the world's developing conditions that perpetually influences everyone and is viewed as one of the significant explanations behind dismalness and mortality over the globe. As of late, the World Health Organization (WHO) has recorded 18,078,957 new reports of malignancy (Dorak and Karpuzoglu, 2012). There are epidemiological investigations on malignant growth that have measurably settled that death rates of grown-ups are higher when contrasted with youngsters and that females are more probably affected (Nomellini et al., 2018). Currently the 6th most frequently occuring malignancy type is head and neck carcinomas. The site of event for head and neck carcinomas incorporate the nose, lips, mouth, throat, larynx and salivary organs. Head and neck carcinomas are normally present as an ailment that locally propels and regularly advances including the cervical lymph nodes (Gutiérrez- Venegas et al., 2020). The phases of advancement of disease happen in a successive way. It starts as hyperplasia and advances to dysplasia, serious dysplasia, arrives at carcinoma in situ stage, and at last outcomes is SCC (Sarode et al., 2017). Larger part of head and neck tumors, practically 90% of the classification, are known to be epidermoid in origin.

One of the main hazard elements of squamous cell carcinoma of the tongue is utilization of tobacco in its numerous structures. Studies have detailed that tobacco clients represent 8 in each 10 patients influenced by oral malignant growth. Tobacco contains various cancer-causing agents. These cancer-causing agents

are available in unfavorable fixations that bring about advancement of malignant growth. Polycyclic fragrant hydrocarbons, nitrosamines and unpredictable hydrocarbons are a portion of the cancer-causing agents present. Liquor utilization has additionally been ascribed to as a causative factor for improvement of malignant growth (Sankaranarayanan et al., 2016). Studies likewise propose that nourishing insufficiencies especially nutrients An and C, zinc, iron may factor being developed of oral disease. Contaminations of viral cause including human papillomavirus (HPV) (types 16 and 18) influence probability of oral malignant growth as proof recommends HPV- positive patients don't passage better as far as endurance rate in a multi year time span in examination HPV- negative patients(Gutiérrez- Venegas et al., 2020)

Chemotherapy for oral malignant growth starts with patients accepting high- dose radiation treatment for extensive stretches one after another, around 6–7 weeks. Patients at stage III or IV patients will probably be regulated EGFR blockers and moreover experience chemotherapy (Kraaijenga et al., 2016). This line of treatment brings about a huge number of reactions to be specific torment, trouble in gulping and ingestion, queasiness, expanded helplessness to contaminations, mucositis because of dryness of mouth, and weariness. Patients with lymph hub association may be dependent upon extraction of the influenced cervical lymph hub. Subsequently patients experience inflexibility of the neck territories, fixed status of the shoulders now and again, xerostomia, modification in taste sensation, weakness of hearing and osteonecrosis ((Dai et al., 2014);(Loorents et al., 2016)). Cetuximab is routinely utilized, however disadvantages incorporate expanded torment sensation and significant expense constraining its accessibility (Dai et al., 2014).

More up to date analyzes for the most part center around in vitro and in vivo examinations to assist better with getting malignancy and build up a novel treatment routine to conceivably forestall the reactions of present disease medicines. Current trends in research focus on therapeutic effects of many substances (Ashwini and Anitha, 2017; Karthiga et al., 2018; Lakshmi et al., 2015; Rajeshkumar et al., 2018a), its effects on the human tissues (Ezhilarasan, 2018; Ezhilarasan et al., 2018; Gheena and Ezhilarasan, 2019; Mehta et al., 2019) and in particular on cancer cells (Ashwini et al., 2017; Lakshmi et al., 2017a, 2017b; Menon et al., 2018; Perumalsamy et al., 2018; Rajeshkumar et al., 2018b; Sharma et al., 2019). Such investigations that mean to find elective medications have tried substances like flavonoids to guarantee maintaining a strategic distance from symptoms like harm to solid tissue and organs, male pattern baldness, and stripping skin. Flavonoids comprise of more than 5,000 polyphenol mixes. They have a diphenylpropane (C6C3C6) carbon spine. The structure of flavonoid can be portrayed as a carbonated 15-carbon spine with two phenyl rings (An and B) notwithstanding a heterocyclic ring (C) (Panche et al., 2016). Flavonoids can be partitioned into 6 kinds based on the example of association of their hydroxyl gathering and their status of alkylation or glycosylation. The sorts are in particular flavones, flavonols, flavanols, flavanones, anthocyanidins, and isoflavones which are constituents of ordinary eating routine. The solvency of flavonoids in water is supposed to be low and is gigantically reliant on the pH. Contingent upon the dissolvable being utilized the dissolvability of flavonoids shift extraordinarily with numerous investigations proposing that their solvency increments in dimethyl sulfoxide. Studies still can't seem to decide the connection between's hydrophobic nature of flavonoids and their solvency (Gutiérrez- Venegas et al., 2020)

FLAVONOIDS

Flavonoids are a gathering of normally happening substances with variable phenolic structures. They are essentially found in natural product, grains, bark, vegetables, roots, blossoms, tea, wine, and stems (Middleton, 1998). The Western eating regimen is said to incorporate blended flavonoids and are

expended for roughly 1 g routinely in a day. In view of various exploratory creature examines, different wellbeing elevating properties are ascribed to flavonoids. The fundamental compound structure of flavonoids is the flavan core, a skeleton containing 15 carbon molecules organized in three rings (C6–C3–C6); two sweet-smelling rings (An and B) associated by a three-carbon-particle heterocyclic ring and an oxygen-containing pyran ring (C). The principle classes of flavonoids incorporate flavonols, flavanols, flavones, flavanones, isoflavones and anthocyanidins and they contrast in the degree of oxidation and immersion of the C ring, while singular mixes inside a class change in the replacement example of the An and B rings (supplements).

The significant impacts of flavonoids incorporate mitigating, antiviral, hostile to hypersensitive, and anticancer (Middleton and Kandaswami, 1994). In excess of 4000 assortments of flavonoids have been distinguished. A few flavonoids likewise have cell reinforcement and nutrient C saving movement (de Groot and Rauen, 1998). It is evaluated that there is a huge decline in the mortality of cardiovascular illnesses and the admission of flavonoids inferable from the french Catch 22 related with high immersed fat admission and red wine utilization .

Antiatherosclerotic effects

Flavonoids have significant effect on the vascular framework because of their cell reinforcement properties where low thickness lipoproteins are oxidized by oxygen radicals and causes endothelial injury and advances atherosclerotic changes (Hertog et al., 1995) Studies have detailed that dementia can be forestalled by the ordinary admission of red wine, which contains flavonoids. Therefore customary utilization of flavonoids may lessen the danger of death from coronary heart infections (Orgogozo et al., 1997).

Antiosteoporotic effects

Studies that analyzed the mineral thickness of bone between ladies who devoured tea and the individuals who didn't inferred that ladies who expended tea had higher mineral thickness of bone . The flavonoids which is available in tea may be ascribed for the anticipation of osteoporosis (Hegarty et al., 2000).

Anti-inflammatory effects

The specific instrument by which flavonoids restrain calming compounds isn't comprehended. Quercetin, a sort of flavonoids, represses cyclooxygenase and lipoxygenase pathways, which hinders the arrangement of these incendiary metabolites. Flavonoids additionally repress eicosanoids biosynthesis, cytosolic and layer tyrosine kinase. at the point when these proteins are restrained, it brings about restraint of uncontrolled cell development and expansion (Yoshimoto et al., 1983). Hindrance of neutrophil degranulation is another significant impact of flavonoids. It pulls back the arrival of arachidonic corrosive by different resistant cells and neutrophils (Kim et al., 1998; Yoshimoto et al., 1983).

Anti-thrombogenic effects

Flavonoids, such as kaempferol, quercetin, and myricetin are known to be successful inhibitors of platelet aggregation. Flavonoids are predominantly antithrombotic as they directly diminish free radicals and inhibit cyclooxygenase and lipoxygenase pathways (Gryglewski et al., 1987). The most important effect of flavonoids is considered to be the inhibition of thromboxane A2 formation (Alcaraz and Ferrándiz, 1987).

Antiviral effects

The infections that might be influenced by flavonoids are respiratory syncytial infection, herpes simplex infection, parainfluenza infection, and adenovirus. Flavonoids have been created as an enemy of HIV specialists in the previous two decades. In vitro explores anyway have demonstrated no away from to the treatment of HIV – tainted patients (Vlietinck et al., 1998)

Antibacterial effect

Studies demonstrated that propolis had an antibacterial effect on the isolated oral streptococci and salivary bacterial counts in vitro. It has been stated that the action of flavonoids can possibly control dental caries (Steinberg et al., 1996).

ANTICANCER POTENTIAL

Various epidemiological examinations recommend that high admission of dietary flavonoids might be related to a diminished danger of malignancy (Le Marchand, 2002). This theory is bolstered by a developing number of in vitro and in vivo examinations, which show flavonoids capacity to repress different phases of carcinogenesis process, to be specific inception, advancement, and movement. In view of these investigations , different components of activity might be included. They incorporate cancer-causing agent inactivation, antiproliferation, cell cycle capture, enlistment of apoptosis and separation, restraint of angiogenesis, antioxidation and inversion of multidrug opposition or a mix of these components. Besides, the promising outcomes from research center and epidemiological investigations have prompted the work of flavonoids in human clinical preliminaries (Ren et al., 2003).

One system by which flavonoids apply their anticancer impact is through cooperation with stage I utilizing chemicals like cytochrome P450 which enacts numerous procarcinogens to receptive intermediates that trigger carcinogenesis. Flavonoids are shown to probably have a job against the enlistment of cell harm by hindering the initiation of cancer-causing agents (Le Marchand et al., 2000). Dysregulated expansion is known to be one of the signs of weakness to neoplasia. Counteraction of disease is typically connected with restraint, inversion or impediment of uncontrolled cell hyperproliferation. Numerous flavonoids have shown restraint of multiplication in many refined human malignant growth cell lines, though they have practically zero poisonous consequences for typical human cells (Pouget et al., 2001);(Wenzel et al., 2000). Aggravation in cell cycle movement may represent the anticancer impacts of flavonoids.Various kinds of malignant growths are related with hyperactivation of CDKs because of transformation of the CDK qualities or CDK inhibitor qualities. Flavonoids actuate cell cycle capture either during G1 or G2/M stage by the hindrance of all CDKs ((Ren et al., 2003); (Wang, 2000)). The critical anticarcinogenic properties of flavonoids might be because of forthright apoptosis (De Vincenzo et al., 2000);(Iwashita et al., 2000);(Sakagami et al., 2000)(Wenzel et al., 2000)(Sakagami et al., 2000).

Flavonoids have exhibited enlistment of apoptosis in some malignant growth cell lines, while saving ordinary cells. The sub-atomic components through which flavonoids cause this enlistment in apoptosis have not yet been distinguished. A progression of late examinations have shown that most chemotherapeutic operators display their tumoricidal impacts by instigating apoptosis of target cells and tissues.

Certain flavonoids cause undifferentiated malignant growth cell lines to separate into cells displaying experienced phenotypic attributes ((Kim et al., 2000);(Mata-Greenwood et al., 2001). Enlistment of terminal separation prompts the resulting disposal of tumor cells and realizes rebalance of ordinary cell homeostasis. Flavonoids are additionally intense angiogenesis inhibitors obtained from common sources. The capacity of specific flavonoids to square strong tumor development might be a result of their restraint of the neo angiogenesis procedure (Sankari et al., 2014). Dietary flavonoids are common cell reinforcements. They act by constraining the harming oxidative response process in cells, which inclines to the improvement of malignant growth (Ren et al., 2003).

FLAVONOLS

Flavonols are found in apples, cranberries, pears, and red grapes. Flavanols incorporate quercetin, kaempferol, myricetin, and morin. Morin can apparently lessen CAL27 cell expansion and relocation (Ji et al., 2018). Morin can essentially lessen quinone reductase action while expanding glutathione S-transferase action in the tongue carcinomas (Gutiérrez- Venegas et al., 2020).
Quercetin prompts putrefaction and apoptosis in SCC9 oral malignant growth cells (Srivastava et al., 2016). Treatment with quercetin either alone or in mix with resveratrol has appeared to repress SCC- 25 cell expansion. In some xenografts contemplates, the mix treatment of cisplatin and quercetin diminished tumor development and diminished oral SCC protection from treatment (Chen et al., 2012). Quercetin additionally hinders movement and attack of the human oral malignant growth cell (Lai et al., 2013). What's more, quercetin stifled development of malignant growth cells and advanced stage G2 cell- cycle capture and apoptosis in EGFR- overexpressing HSC- 3 (Huang et al., 2013). In another investigation, quercetin exhibited cytotoxic impacts on SAS cells and restrained injury conclusion (Lai et al., 2013).

Fisetin actuates apoptosis of (HSC3) human oral disease cells through weight on endoplasmic reticulum and brokenness of mitochondria- mediated flagging pathways (Shih et al., 2017). The fisetin incited apoptotic cell demise in blend with a powerful autophagy inhibitor could be a valuable treatment for oral disease (Park et al., 2019; Su et al., 2017). Fisetin causes acceptance of apoptosis of human oral disease cells (SCC-4) through responsive oxygen species creation, endoplasmic reticulum stress, caspase-, and mitochondria-subordinate flagging pathways (Park et al., 2019; Su et al., 2017).

Kaempferol was accounted for to repress SCC- 4 cell expansion, relocation, and attack by hindering framework metalloproteinase interpretation and interpretation. It likewise hinders articulation of tissue inhibitors of metalloproteinase- 2 and represses phosphorylation of ERK1/2. Rewarding the cells with kaempferol and a MEK inhibitor supposedly advanced decrease of MMP- 2 movement and in this way diminished cell migration (Lai et al., 2013).

Casticin repressed cell development, created cell- cycle capture in stage G2/M, decreased cyclin B1, p53, p21, WEE1, and Cdc25c, expanded Cdk2, checkpoint kinase 2 (Chk2) . it additionally causes apoptosis, brings down mitochondrial layer potential, decreased Bcl- xL and BCL2 levels and expanded the exercises of caspases - 8 and - 9, Fas- associated protein with death area (FADD), Bid, cytochrome c, BAX, and AIF cell development and instigates cell apoptosis in human oral malignancy SCC-4 cells (Chou et al., 2018).

FLAVONES

Flavones incorporate apigenin, luteolin, diosmin and hesperidin. Chamomile, onion, nectar, and mixed drinks, for example, brew and wine are rich wellsprings of apigenin. Apigenin has been accounted for to bring down oral SCC cell endurance rates (Masuelli et al., 2017). Apigenin disables OSCC development in vitro by prompting cell cycle capture and apoptosis. Medicines of apigenin in low portions is a sort of chemotherapy that would help specifically slaughter just those phones which can't react appropriately to incited pressure, similar to malignancy cells, due to their genomic unsteadiness. Capacity of apigenin to go about as a little particle inhibitor by downregulating a few significant proteins associated with the beginning and movement of malignant growth, can be abused in the improvement of new anticancer treatments (Madunić et al., 2018).
Chrysin is a flavone present in nectar and dust (Huang et al., 2016). Chrysin and Luteolin can diminish cell feasibility and DNA biosynthesis in a portion subordinate way (Yang et al., 2008) High centralization of chrysin compares with poor patient visualization and by and large endurance rate (Celińska-Janowicz et al., 2018).

Luteolin decreased tumor development by up to 92% in the past xenograft tests. It was found to diminish cell feasibility in a dose- and time- dependent way in SCC- 4 cells. Luteolin had no impact on CDK levels, however advanced DNA discontinuity and actuated articulation of the pro- apoptotic proteins. When managed along with paclitaxel, luteolin enlarged the cytotoxic impacts of the paclitaxel in SCC- 4 cells (Yang et al., 2008).
Baicalein instigates apoptosis by means of calcium related mitochondrial pathway just as a caspase- 3-dependent pathway. Scutellarin has a wide scope of organic impacts, including anti- inflammatory and anticancer impacts (Goh et al., 2005; Suh et al., 2007). It hindered cell practicality in SAS and HSC- 4 cells in a period and measurement subordinate way (Li et al., 2013).

Diosmin and hesperidin stifled lessens the rate of neoplasms and pre- neoplasms in the tongue. Diosmin and hesperidin were not more when utilized in blend than when either was conveyed alone, showing that they don't act synergistically (Tanaka et al., 1997).

FLAVANOLS

Flavanols are a class of flavonoids that contain an epicatechin or catechin essential structure. They are found in cocoa, red wine, and green tea (Ji et al., 2018). They advance portion subordinate decreases in cell expansion and morphological changes in SCC- 25 cells (Elattar and Virji, 2000). Polyphenols have a synergistic impact and display cytotoxicity and apoptosis (Mohan et al., 2007). EGCG supposedly causes restraint of disease cell expansion and movement while likewise invigorating apoptosis (Li et al., 2018). Furthermore, EGCG restrains SCC cells specially (Yang et al., 2017). EGCG prompts DNA fracture, and apoptosis.epigallocatechin- 3- galato (EGCG) downregulates an enormous number of qualities in SCC25 cells. Apparently EGCG can increment mitochondrial intracellular oxidative pressure bringing about the prompt loss of film potential and enlistment of early apoptosis. EGCG was later appeared to initiate mitochondrial ROS in SCC- 25 and SCC- 9 cells. In SCC- 25 cells, EGCG represses the interpretation, interpretation, and action of sirtuin 3 (SIRT3), a significant mitochondrial redox balance controller (Tao et al., 2015).

FLAVANONES

Flavanones are plentifully found in lemons, oranges, and limes. In 1994, hesperidin was accounted for to forestall 4NQO- induced carcinogenesis (Tanaka et al., 1994). Hesperidin organization decreased the recurrence of tongue carcinoma advancement while ;owering polyamine levels. Hesperidin and diosmin were found to restrain oral carcinoma improvement and furthermore stifle cell expansion (Tanaka et al., 1997). The admission of flavanones likewise brings down the danger of upper aerodigestive tract malignant growths (Rothwell et al., 2017). Acacetin initiates the apoptosis of the oral squamous cell carcinoma cell line (HSC-3) which may go about as a promising restorative specialist for the treatment of OSCC. It diminishes HSC- 3 cell reasonability, expands segment of cells in cell cycle, apoptosis, and initiation of caspase- 3, caspase- 9. It influences mitogen- activated protein kinase- regulated atoms, such as actuating downregulation of BCL- 2and BH3 while expanding the BAX and cytochrome c levels (Kim et al., 2015).

ANTHOCYANIDINS

Anthocyanidins are a gathering of water- soluble shade atoms that give red- orange tinge to blue- violet colors in organic products, vegetables, and grains. Studies revealed that grape seed proanthocyanidins restrained the suitability of various squamous cell carcinoma cells. They additionally repressed cyclins and CDKs and upregulated apoptosis (Prasad and Katiyar, 2012). Also, when given as a food supplement, anthocyanins restrain tumor development of SCC- 1. This hindrance is ascribed to decreased cell expansion, expanded apoptosis, diminished articulation of cyclins, CDKs yang 2017.

ISOFLAVONES

Isoflavones are portrayed by a fragrant replacement at carbon C3. They are available generally in soybean and viewed as phytoestrogens. Isoflavones incorporate genistein, daidzein, glabridin, and biochanin A . Naringenin is the forerunner particle to genistein. Genistein supposedly lessens SCC- 25 cell multiplication, actuates cell- cycle capture without influencing apoptosis. Genistein additionally stifles COX- 2 movement and diminishes prostaglandin E2 levels (Ye et al., 2004). Glabridin seems to decrease SCC- 9 and SAS cell reasonability in a period and portion subordinate way. The chemopreventive movement of glabridin has been connected to the JNK pathway, despite the fact that glabridin directs the enactment of ERK1/2 and p38 (Chen et al., 2018) (Chen et al., 2018).

CHALCONES

The chalcones (1,3- diphenyl- 2- propen- 1- ones) are antecedents to flavonoids and isoflavonoids of yellow- orange hue. The chalcone licochalcone An is available in licorice and has a scope of impacts including anti- inflammatory, antimicrobial, and cell reinforcement exercises. Licochalcone An apparently lessens SCC- 25 cell feasibility in a time- and dose- dependent way. Isoliquiritigenin (ISL) hinders cell expansion, movement, attack and diminishes ROS creation (Hou et al., 2017).

FLAVOLIGNINS

The flavolignin, silymarin is extricated from thorn and has low water dissolvability. Silymarin is known to lessen dysplasia, increment stage 2 detoxification compounds, and decrease prostaglandin and polyamine levels. Likewise, they additionally hinder cell multiplication and initiated caspase- dependent apoptosis in HSC4 cells (Yanaida et al., 2002).

CONCLUSION

Numerous chemotherapeutic specialists act against tumor cells without saving typical cells. This remaining parts a significant obstruction alongside advancement of multidrug opposition limits chemotherapy in malignant growth. The promising outcomes displayed by flavonoids in various in vitro and in vivo investigations will invigorate the advancement of flavonoids for malignant growth chemoprevention and chemotherapy. Anyway clinical preliminaries accessible have required intravenously controlled flavonoids before huge impacts are seen. These focuses are probably not going to be accomplished utilizing the dietary enhancements at present accessible. Along these lines, increasingly engaged clinical investigations are required to build up whether such dietary flavonoids can be misused to accomplish malignant growth preventive or remedial impacts in people.

AUTHORS CONTRIBUTION

All the authors have equally contributed to the design ,conceptualization and implementation ,Proof reading of the manuscript .

CONFLICT OF INTEREST

Nil

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