Archives of Advances in Biosciences

Review Article:

A Review on Flavonoids as a Potential Biomolecule for Inhibiting the Effect of Head and Neck Cancer

Sara Ikram[1], Muhammad Moazzam Ashraf [1*], Mudasir Hussain[2], Sidra Shaheen[1], Muhammad Shaoib[3]

1.Department of Biotechnology, Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan
2.Soonchunhyang Institute of Medi-bio Science, Soonchunhyang University, Chungnam-do, Republic of Korea
3.Department of Chemistry, Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan

Cite this article as: Ikram, S., Ashraf, M. M., Mudasir Hussain, Sidra Shaheen, & Muhammad Shaoib. (2024). A Review on Flavonoids as a Potential Biomolecule for Inhibiting the Effect of Head and Neck Cancer. *Archives of Advances in Biosciences, 15*(1), 1–12. https://doi.org/10.22037/aab.v15i1.46931

https://journals.sbmu.ac.ir/aab/article/view/46931

Article info:
Received: 26 Nov 2024
Accepted: 02 Dec 2024
Published: 10 Dec 2024

*** Corresponding author:**

Muhammad Moazzam Ashraf, PhD.

Address: Department of Biotechnology, Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan

E-mail:
moazzamsh4@gmail.com

Abstract

Context: Cancer is one of the most significant, complex, and long-term diseases, characterized by uncontrolled cell multiplication, affecting millions of people around the globe. Developed countries are considered to experience higher incidence and mortality rates due to cancer. Cancer affects various body parts including the liver, breast, lungs, bladder, rectum, prostate, blood, and head and neck. Head and neck cancer is the seventh most prevalent cancer globally, typically arising from tissues of the mouth, larynx, pharynx, trachea, throat, and salivary glands.

Evidence Acquisition: Different factors can cause cancer, such as the use of tobacco, alcohol, genetic alterations, and other environmental factors. Treatment is a challenging part due to the disease's progression and potential side effects on normal body functions. Current treatments such as chemotherapy have limitations due to their toxic effects on other normal body cells. Therefore, the need for less toxic and more selective treatment arises. Natural phenolic compounds, such as flavonoids derived from plants, fungi, and bacteria, have shown promising potential in the treatment due to a higher therapeutic index and low toxicity level. Flavonoids reduce cancer cell growth, inhibit cancer development enzymes, and regulate apoptosis-related proteins, transcription factors, and pathways. Several studies have shown that their anti-cancer properties have made them effective against head and neck cancer cells.

Results: Plants have been major sources of flavonoids but fungi, especially endophytic fungi are also valuable sources of natural therapeutic agent flavonoids. Extraction of flavonoids from fungi offers a sustainable and environmentally friendly approach, eliminating the need for land, water, and fertilizer. Furthermore, fungi can yield higher amounts of flavonoids than other sources.

Conclusion: Further research in medical applications of flavonoids as biological therapeutic agents could potentially reduce the impact of the disease.

Keywords: head and neck cancer, flavonoids, bioactive molecule, endophytic fungi

1. Context

Cancer remains one of the greatest challenges in modern medicine, affecting millions of people worldwide [1]. According to the study of [2], cancer is among the leading causes of global mortality; it kills one in six people as of 2021. Anticipatory research may indicate that new cancer cases could progressively rise to 12. 10 million a year within the next decade, with this trend continuing to

increase [3]. IARC in 2018 attributed 7. 6 million cancer deaths all over the world . Cancer in developed countries presents higher incidence and mortality rates; it is estimated that 63% of total cancer deaths occur in developed countries [4]. For years, the WHO has pinpointed it as one of the primary causes of death in various countries and pointed to its greater standing than other significant killers such as stroke and coronary heart disease [5]. Some of the drivers of global cancer incidence include population growth and ageing [6]. These aspects increase the incidence and fatalities of cancer and hence it becomes more paramount to address this public health problem [7]. Accompanying the multiplication of cells is cancer, which is regarded as a long-term [8], non-communicable [9], and complex ailment. Cancer classes are distinguished by the areas of the human body in which they occur such as lung, breast, skin, prostate, colon, rectal, bladder, corpus uteri, thyroid, head, and neck [10-11] . The IARC has classified head and neck cancer as the seventh most prevalent cancer present globally [12]. More than 1 million new cases were documented in 2016 [13]. These cancers develop from epithelial tissues of the oral cavity, throat, pharynx, and larynx [14]. Premising risk factors include the use of tobacco and ethanol [15], which contribute to 75 per cent of the cases [16], which is due to the presences of harmful elements in alcohol and tobacco [17]. HPV infection also raises the risk especially for oropharyngeal site cancers [18-20]. The regions of upper respiratory and digestive tract are mostly affected due to head and neck cancer [21]. It has been established that patients diagnosed with H&N cancer are more at risk of developing SPCs in the same anatomical subsites [22]. Patients diagnosed with HNC have an increased predisposition to develop SPCs in HNC-related sites. Physical and chemical carcinogens present in the environment can influence the cytoplasm and nucleus of the cell through direct or mediated influence, which in turn causes alterations in the genes and DNA to cause cancer [23]. Another major hurdle in eradicating the menace of cancer is that most of the drugs in the market have low potential [24], this can be solved by taking potential therapeutic drugs. Head and neck cancer signs and symptoms include; mucosal changes, weight loss, tongue pain, pain in the throat, ulceration formation and neck swelling [25]. The treatment of head and neck cancer, hence, poses a challenge due to its stage of development. Furthermore, signs and symptoms can be mucosal changes, unexplained weight loss, odynophagia, dysphagia, ulcerative lesions, and neck discrete. These cancers are therefore not easy to manage, hence the need for the development of new therapeutic regimens that would effectively fight these cancers.

The existing modes of cancer treatments, especially chemotherapy, have certain challenges although they are effective [26]. Chemotherapeutic drugs used to eliminate growing tumor cells have toxic effects that affect normal cells by producing reactive oxygen species; common side effects range from fatigue, nausea, and hair loss [27]. Thus, the requirement is for less toxic treatments, which will selectively target cancer cells. This made the biological drugs particularly those sourced from natural products such as plants, fungi, and bacteria have a high therapeutic index with low toxicity [28-29]. Moreover, various bioactive compounds affect the health of humans, and they also have the potential for cancer treatment in which flavonoids are one of them [30].

Table 1. Global Cancer Incidence and Mortality

Region	Cancer Incidence	Cancer Mortality	Factors Contributing to Cancer
Worldwide	Rising to 12.10 million cases	7.6 million deaths	Population growth, ageing, environmental carcinogens, lifestyle factors
Developed Countries	Higher incidence and mortality	63% of total cancer deaths	Advanced diagnostic methods, lifestyle factors

Developing Countries	Lower incidence and mortality	37% of total cancer deaths	Limited access to healthcare, late-stage diagnosis

Table 2. Types of treatment methods, their and benefits sources

Treatment Type	Source	Benefits	Examples
Chemotherapy	Synthetic drugs	Kills cancer cells, slows tumor growth	Doxorubicin, Cisplatin

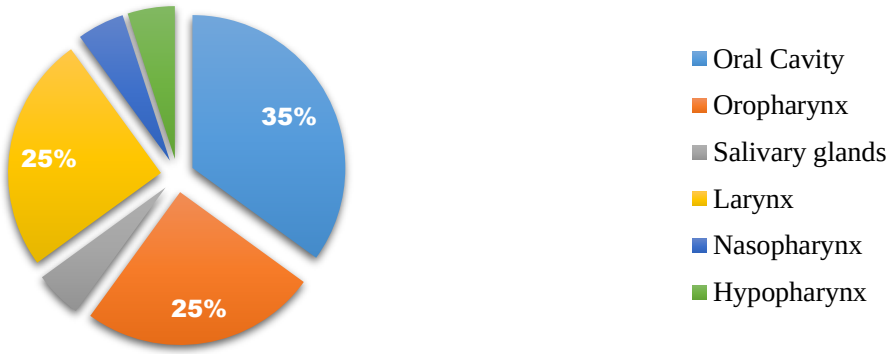

Figure 1. The ratio of distribution of cancer in affected regions of head and neck

Treatments in Head and Neck Oncology

Head and neck cancers encompass a diverse group of malignancies that can affect various areas such as the mouth, throat, larynx, sinuses, and salivary glands. Treatment options vary depending on the location, stage, and overall health of the patient. Below is an overview of the current treatment standards for head and neck cancers:

Surgery: Surgery is often the first line of treatment for head and neck cancers, particularly when the tumor is localized and operable [31]. The goal is to remove the cancerous tissue while preserving as much function and appearance as possible. This typically involves removing the tumor along with a margin of surrounding healthy tissue, and in cases where the cancer has spread, it may also include the removal of lymph nodes in the neck. Reconstructive surgery may be required post-tumor removal to restore function or appearance. Surgery can result in significant changes in appearance, difficulty swallowing, and speech impairments, depending on the location of the tumor [32]. It may also cause nerve damage, leading to reduced sensation or movement in certain areas.

Radiotherapy: Radiotherapy uses high-energy radiation to target and destroy cancer cells. It can be used as a primary treatment or in conjunction with surgery and chemotherapy [33]. The most common type of radiotherapy is external beam radiation therapy (EBRT), where radiation is delivered from outside the body. Intensity-modulated radiation therapy (IMRT) is a more advanced form of EBRT that allows for precise targeting of the tumor while minimizing damage to surrounding healthy tissue [34]. Radiotherapy can cause skin irritation, fatigue, dry mouth (xerostomia), difficulty swallowing, and changes in taste. Long-term effects may include damage to the salivary glands, resulting in chronic dry mouth and an increased risk of dental problems [35].

Chemotherapy: Chemotherapy involves the use of drugs to kill cancer cells or stop their growth. It is often used in combination with radiotherapy (chemoradiation) to enhance the effectiveness of

treatment, especially in more advanced cases. Platinum-based chemotherapy drugs like cisplatin and carboplatin are commonly used, either alone or with other chemotherapy agents [36]. Chemotherapy can lead to a range of side effects, including nausea, vomiting, hair loss, fatigue, and an increased risk of infections due to lowered blood cell counts. Neurotoxicity and kidney damage are also possible with platinum-based chemotherapy [37].

Immunotherapy: Immunotherapy is a newer treatment modality that helps the body's immune system recognize and attack cancer cells. It has shown promise in treating head and neck cancers, particularly those that are resistant to other treatments. Checkpoint inhibitors such as pembrolizumab and nivolumab are used to block proteins that prevent the immune system from attacking cancer cells [38]. While generally well-tolerated, immunotherapy can cause immune-related side effects such as skin rashes, colitis, hepatitis, and thyroid dysfunction. Severe cases may lead to life-threatening inflammation of organs.

Targeted therapy: Targeted therapy involves drugs that specifically target molecules involved in the growth and spread of cancer cells. These therapies are designed to spare normal cells, potentially reducing side effects compared to traditional chemotherapy. A common targeted therapy for head and neck cancers is cetuximab, an EGFR inhibitor that targets the epidermal growth factor receptor (EGFR), which is often overexpressed in these cancers [39]. Common side effects of targeted therapy include skin rash, diarrhea, and low magnesium levels. Unlike chemotherapy, these side effects are usually more manageable, but they can still impact the patient's quality of life.

Photodynamic therapy (PDT): Photodynamic therapy (PDT) is a less common treatment that involves the use of light-sensitive drugs and laser light to destroy cancer cells [40]. It is mainly used for early-stage cancers or for treating areas where surgery might cause significant functional impairment. PDT can cause skin sensitivity to light, swelling, and pain in the treated area. Additionally, it may not be as effective for larger or deeper tumors.

Palliative Care: For advanced-stage head and neck cancers that may not be curable, palliative care focuses on relieving symptoms and improving the quality of life. This can involve pain management, nutritional support, and psychosocial care [41]. Palliative care itself does not have side effects, but the underlying treatments, such as pain medication, may cause side effects that need to be managed, including drowsiness, constipation, or dependence on drugs.

Flavonoids

Natural polyphenolic compounds are known as flavonoids [42]. They are polyphenolic compounds, and their structure contains 15 carbons in a configuration of C6-C3-C6 [43], forming two benzene rings that are connected by a central oxygen heterocyclic ring [44] found in herbs, grains, vegetables, fungi and actinomycetes. All over the world, there are almost 6000 flavonoids, with the majority of flavonoids found in higher plants, actinomycetes and fungi [45]. Flavonoids act as secondary metabolites, and they impact different diseases like Alzheimer's, cancer, and atherosclerosis diseases [46]. They are widely used for their characteristics such as anti-cancer, antioxidant, antiviral and anti-inflammatory properties [47-48]. These compounds reduce the growth of cancer cells, their spread to other parts of the body, and promote cancer cell death by inducing apoptosis [49-50], reducing the proliferation of cells and interfering with pathways of signal transduction. Currently, flavonoids have exhibited a strong potential as anticancer agents in cancer prevention and treatment due to their ability to modulate multiple signal transduction pathways to prevent the proliferation of tumor cells and their metastasis [50]. They induce apoptosis in cancer cells, inhibit cell division and interfere with the important signal transduction pathways responsible for cancer cell development. Flavonoids' capacity to influence various cellular activities including oxidative stress and inflammation which are known to play a role in carcinogenesis further augments their use in drug development. Thus, flavonoids may have significant potential as an adjunct in Oncology medicine by working through the several pathways that are involved in carcinogenic processes.

Cancer has been illustrated to be responsive to flavonoids in different ways, the most significant being the interference with the various phases of cancer development [51]. The mechanisms of action of these compounds include antioxidant properties which assist in combating reactive oxygen species (ROS) that cause damage to the DNA and lead to the development of cancer [52]. Flavonoids' most important cancer-fighting mechanism is their effect on triggering programmed cell death in cancer cells. Apoptosis is a precisely regulated physiological process and its regulation is lost in most cancers so that the cancerous cells do not undergo apoptosis and therefore do not die [53]. Consequently, flavonoids have been found to induce apoptosis through such mechanisms as caspase activation and alteration of pro-apoptotic and anti-apoptotic proteins within the cell. Flavonoids may decrease cell proliferation through cell cycle arrest in different phases thus

hindering the proliferation of cancer cells. They achieve this through modulating cardinal signal transduction pathways implicated in cancer such as the PI3K/Akt, MAPK, and NF-κB pathways. Flavonoids act on the pathways that affect the viability of the tumor cells and the ability of the cancer cells to create new blood vessels required to nourish the tumor or to spread to other parts of the body. Flavonoids, quercetin, luteolin, and EGCG have been found to play a prominent role in preclinical studies in inhibiting tumor growth and improving the effectiveness of conventional cancer treatment that includes chemotherapy and radiation therapy [54]. These compounds have been identified to render cancerous cells more vulnerable to obliteration or destruction and at the same time sparing normal healthy cells from the detrimental effects of treatment. This is quite advantageous for the treatment of cancer because flavonoids can interfere with multiple targets that lead to cancer. The possibility of increasing the effectiveness of the generally applied anti-cancer treatments, along with their low side effects profile, makes them more attractive for use as adjuvants in oncology [55].

Classification

Flavonoids are categorized into six subclasses based on their chemical structures: Flavanones, flavanols, flavonols, anthocyanidins, flavones, and isoflavonoids, among others.

Flavanones: Flavanones are also known as di-hydro flavones and based on the C ring contain a saturated and oxidized structure. Flavanones have saturated C ring without a double bond between positions 2 and 3 and a ketone group at position 4. Their derivatives are mostly found in citrus fruits and are well appreciated because of their healthy qualities such as anti-oxidative properties and the ability to neutralize free radicals [42]. Two common types of flavanone include hesperetin and naringenin [56].

Flavanols: Catechins are another name for flavanols [42], mostly present in bananas and blueberries. The hydroxyl groups at C3 present in this type of flavonoid contributes to their antioxidant property [57]. Flavanols are a subclass of flavonoids generally characterized by the C6–C3–C6 structure, which consists of two aromatic rings, ring A and B, and one heterocyclic pyran ring, ring C.

Flavonols: Flavonols are a subclass of flavonoids that have an unsaturated C ring at C2-C3, while the antioxidant group is located at C4 and at C3 the hydroxyl group is present [42]. They are characterized by a 15-carbon chain that consists of two aromatic rings, ring A and ring B and a C ring that is heterocyclic. One aromatic ring typically has hydroxyl groups at the 5 and 7 positions and other aromatic ring is attached to the C ring at position 2 and can have various hydroxyl or meth-oxy substituents. The Pyran heterocyclic ring includes a double bond between positions 2 and 3, and at position 3 a hydroxyl group is present. The key compounds are quercetin, kaempferol, myricetin, is isorhamnetin and so forth, and are well known for their health promotion [58].

Flavones: Flavones, a subclass of flavonoids, have a 15-carbon structure consisting of two aromatic rings, ring A and B, and a heterocyclic ring C. A double bond exists between positions 2 and 3 on the C ring, and at position 4, a ketone group is present which has biological importance [42].

Anthocyanidins: Anthocyanidins are a class of flavonoids that combine water-solubility with unsaturation and non-oxidants [59]. The basic structure of anthocyanidins includes a 15-carbon skeleton with two aromatic rings, A having hydroxyl groups at the 5 and 7 positions, and ring B with hydroxyl or meth-oxy substituents, and a heterocyclic ring C, between positions 2 and 3 that contains an oxygen atom. Anthocyanins have antioxidant actions in their chemical structure, mainly through the phenolic ring, and because of the presence of multiple hydroxyl groups located at ring C (position 3) and at the 3', 4' and 5' positions on ring B within the molecule [60].

Isoflavonoids: Isoflavonoids can be found in plants, actinomycetes and fungi. Consumption of isoflavonoids has shown a reduction in certain types of cancer related to estrogen. This class of flavonoid contains 15 carbon atoms and is different from other classes because of its unique B ring attachment at the C3 position of the heterocyclic C ring, whereas, in other classes of flavonoids it attaches to C2 position. It occurs mainly in soybeans and plants of the Leguminosae family, these compounds are comparatively scarce but are endowed with rather special biological attributes [61].

Table 3. Classes of flavonoids and their sources

Flavonoid Class	Chemical Structure	Sources	Key Properties	Examples
Flavanones	Saturated and oxidized C ring	Citrus fruits	Anti-oxidative, neutralize free radicals	Hesperetin, Naringenin
Flavanols	Hydroxyl groups in position C3	Bananas, blueberries	Antioxidant activity	Catechin, Epicatechin
Flavonols	Unsaturated C ring at C2-C3	Onions, kale, broccoli	Health enhancement, antioxidant	Quercetin, Kaempferol
Anthocyanidins	Water-soluble, no oxidants	Berries, red cabbage	Antioxidant actions	Cyanidin, Delphinidin
Flavones	The double bond between C2-C3	Parsley, celery	Biological importance	Apigenin, Luteolin
Isoflavonoids	Mainly in soybeans	Soybeans, legumes	Special biological attributes	Genistein, Daidzein

2. Evidence Acquisition

This review article utilized popular search engines such as Google, PubMed, Google Scholar, Scopus, ProQuest, and Web of Science to explore the topics of "head and neck cancer", "flavonoids", "bioactive molecule" and "endophytic fungi".

3. Results

Classification Properties of flavonoids against head and neck cancer cell

Anti-cancer properties of flavonoids: The existing cancer treatments such as chemotherapy, radiotherapy not only eliminate the cancer cells from body but also damage the normal body cells, which can even cause more adverse effects on overall individual's health. Cancer is a process involving multiple stages where initiation, progression, and development of cancer take place. Flavonoids have been shown to decrease the proliferation rate of developing cancer cells in the pharynx [62]. Enzymes that are involved in cancer development, such as protein-kinases –enzymes involved in phosphorylation regulated various cellular functions – can become dysregulated, resulting in uncontrolled cell division. Topoisomerase, which is involved in the proliferation of cancer cells by managing the topology of the DNA of cancer cell [63] when targeted by inhibitors or chemo-drugs may cause several side effects such as cardiovascular dysfunction, development of resistance against drugs in cancer cells and hepatotoxicity. Flavonoids, on the other hand, provide a safer approach by binding to ATP binding sites of protein-kinases, inhibiting its activity, and by binding to the topoisomerase, preventing the re-ligation of DNA of cancer cells which results in cancer cell death.

Inducing Cell Apoptosis in HNC cells: Apoptosis is a cellular mechanism involving programmed cell death. Flavonoids can target cancer cell by inducing apoptosis via multiple mechanisms, such as regulating apoptosis related proteins such as Caspases, altering transcription factors such as NF-$_k$B and p53 and modifying pathways such as PI3K/AKT/mTOR

pathway and PI3K/Akt/FOXO3 pathway [64]. A study by [65] shows that several classes of flavonoids, like Quercetin and Kaempferol, have shown a reduction in melanoma cells, showing the ability of flavonoid to regulate proteins responsible for the survival and death of cell. Quercetin and Kaempferol have also been shown to decrease the caspase3, bax, and p53 levels, associated with cell apoptosis, and inhibited expression of Bcl-2, a protein that promotes the survival of cancer cell which shows the contribution of flavonoid to anti-cancer effects [66]. explained the significant anti-cancer effect of kaempferol and fisetin, types of flavonoids, on head and neck cancer cell lines by inhibiting the proliferation of SCC-9, SCC-25, and A-253 HNC cells, kaempferol and fisetin also inhibited Bcl-2, an anti-apoptotic protein, and disrupted the mitochondrial transmembrane potential, ultimately inducing the apoptosis in HNC cells.

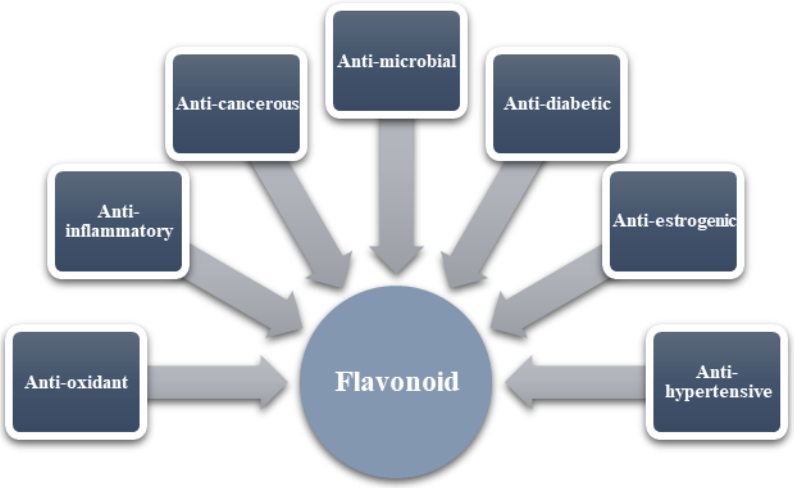

Figure 2. Biological properties of flavonoids

Antioxidant properties: Reactive oxygen species (ROS) act as cellular messengers, but they can also cause damage to cells when their numbers increase. Flavonoids, because of their structure, have shown antioxidant properties by preventing the oxidative stress and neutralizing the free radicals that damage proteins [67]. Flavonoids reduce the formation of reactive oxygen species (ROS) by donating a hydrogen atom and an electron, which forms a stable flavonoid radical. The ring B present in structure of flavonoid is more electron-rich than the ring A, which particularly attracts free radicals and selectively interacts with them. Some studies also suggested that flavonoids may have the potential to induce excessive oxidative stress, which may lead to the death of cancerous cells [68].

Fungi as a source of flavonoids

Fungi have great potential in the production of these compounds. Like plants, many endophytic fungi also synthesize flavonoids [69]. These fungi are intercellular and intracellular inhabitants of plant tissues that do not result in pathogenicity and synthesize multiple bioactive compounds such as flavonoids, and similar compounds; keto-flavonoids [70]. Moreover, the world is estimated to be home to more than 3 million different types of fungi, but only a small portion of them have been domesticated or investigated and are recognized as potential sources of numerous therapeutic molecules [71-72]. Thus, endophytic fungi are other significant sources of bioactive compounds that can act as anti-cancer agents [73]. In endophytic fungi, the concentration of flavonoids is high as suggested in different research. Drugs derived from bioactive derivatives of endophytic fungi are less toxic have better efficiency, and effectiveness, and are cost-effective as well compared to chemical pesticides [74]. Nevertheless, since they reside within plant tissues, endophytic fungi can synthesize flavonoids as secondary products [75].

Compared to the extraction of plant flavonoids, the extraction from fungi has the following advantages. From a commercial production viewpoint, it is desirable because it maintains consistent production of beneficial compounds. Under laboratory conditions, flavone production may be standardized and scaled up so that the constant supply of these compounds can be provided for study or application; the advantage again lies in the easy manipulability of fungal cultures when compared to that of insects [76]. Fungi can also be

genetically modified or altered [77] to increase flavonoid synthesis or alter the structure of these compounds, creating new opportunities for the development of flavonoids with preferred bioactivities Besides, the synthesis of flavonoids from fungi could be more resource-friendly and efficient than using agricultural plants, which need land and water among other resources. This means that the sources of fungi are viable for flavonoid extraction considering the modern world's shift to sustainable and environmentally friendly ways of extracting natural compounds. According to [78] and [79], the endophytic fungal species; *Alternaria alternate* has abilities to synthesis flavonoids within its host plants. *Alternaria alternate*, classified as the kingdom of fungi and the specific genus of Alternaria, is distributed widely and has multiple ecological characteristics about plant hosts. It is well known to a layman for its dual nature that makes it to be both a pathogen and an endophyte and hence has varying interactions with its host organism [80-81]. It can synthesize biologically active metabolites [82]. Multipurpose fungi *Alternaria alternate* is known as a pathogen and endophyte with different biologically active compounds. It is important to note that the experimentation of this fungus can only be done at a laboratory scale, where the fungus grown, and its flavonoids extracted and purified. The extracted flavonoids will be examined for their potential to cause cell death in head and neck cancer cell lines. The most effective flavonoid would be subjected to further study in the search for an anti-cancer drug. The antitumor properties of flavonoids isolated from fungi can provide a novel approach to the long-standing problem of finding more effective cancer treatments that have few side effects, a significant goal in contemporary oncology.

4. Conclusion

Cancer remains a problem in current society, it is widespread and contributes to a large number of mortality cases. This observation is evident by the projected increased health risk of cancer incidents which elucidates the increasing importance of adopting new therapeutic strategies. Among all cancers, head and neck cancers are challenging and require specialized treatments caused by factors such as tobacco use, alcohol consumption, and HPV. Chemotherapy remains one of the current treatments and it has brought social menace through its side effects hence justifying the search for more effective compounds without toxic effects. Among phytochemicals, the recent focus has been towards flavonoids which are natural polyphenolic compounds present in a variety of plants and fungi due to their anticancer activity, and antioxidant and anti-inflammatory characteristics. These compounds can suppress the growth of cancer cells trigger cancer cell death, and act on signal transduction networks; this can open new safer and more effective treatment paradigms in cancer therapy. The extraction of flavonoids from fungi like endophytic fungi is a new and efficient way which might help in increasing efficiency and also, which would not have any published negative impacts on the environment. More investigations in combination with medical uses of flavonoids could give a shift in the treatment of cancer and may help to decrease the magnitude of this menace in the future. As the result of further research on the application of flavonoids in the treatment of certain diseases, patients are likely to have better treatment with fewer side effects, thus paving the way for better health and quality of life of the patients.

Ethical Considerations

Compliance with ethical guidelines

This article is a review with no human or animal sample.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Author's contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declare no competing interests.

Acknowledgments

None.

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