A Comprehensive Review on Anti-Cancer Properties of *Amaranthus viridis*

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**ABSTRACT**

*Amaranthus Viridis* Linn (Family Amaranthaceae) commonly known as “Chowlaí” which a common name. *A. Viridis* contains several compounds like Quercetin, Kaempferol, Hydroxycinnamic acids (HCs) (coumaric acid, ferulic acid, sinapic acid, caffeic acid, chlorogenic acid, rosmarinic acid), Syringic acid (SA), Rutin, Vitexin, Vanillic acid, etc. In search of new activities and chemical entities, phytochemical screening of the extract from leaves of *A. Viridis* L. indicates the presence of biologically active constituents saponins, tannins, phenols, flavonoids, alkaloids, cardiac glycoside, steroids, and triterpenoids. Quercetin is the aglycone form of several other flavonoid glycosides, Kaempferol (3,4′,5,7-tetrahydroxyflavone) is a natural flavonol, a type of flavonoid, Syringic acid (SA) is a phenolic compound of natural origin. Syringic acid (SA) is an excellent compound to be used as a therapeutic agent in various diseases (diabetes, CVDs, cancer, cerebral ischemia, neuro and liver damage) and possesses anti-oxidant, antimicrobial, anti-inflammatory, and antiendotoxic activities. Vitexin (apigenin-8-C-glucoside) has also shows the wide range of pharmacological effects, including but not limited to anti-oxidant, anti-cancer, anti-inflammatory, and neuroprotective effects. Vanillic acid shows the anti-cancer activity.

**Keywords**- Anti-oxidant, Anti-cancer, Anti-inflammatory, Neuroprotective effect, Flavonoid, glycoside, phenolic compound.

I. INTRODUCTION

*Amaranthus Viridis* Linn (Family Amaranthaceae) is distributed in the warmer parts of the world [1,2]. Traditionally it is eaten as a leafy vegetable in south India. The leaves and seeds are highly nutritious. The nutrients present in the leaves include fiber-containing vitamins. A, B, B2, C Minerals like calcium, phosphorous, iron, amino acids like arginine, histidine, lysine cystine, methionine, phenylalanine, leucine, isoleucine, threonine, tryptophan, tyrosine, valine. The seeds also contain protein and fat. Therefore the *A. Viridis* contain a high nutrient value. In Nepal, the seeds have been used to reduce labour pain and treat stomach problems [3,4]. A poultice of leaves is used to treat the inflammation, boils, and abscesses. In India, it is used as an antidote for snake bites and scorpion stings. Other traditional uses are diuretic, anti-rheumatic, antulcer, laxative, antileprotic, anticancer, and also used to treat respiratory problems. Entire plant decoction is used to treat dysentery and inflammation [5,6]. The juice of root *A. Viridis* is used to treat the inflammation during constipation and urination [7,8]. The plant is used as vermifuge and emollient [9,10]
II. SYNONYMS

➢ Various more names for Amaranthus viridis L. include [12,13]
  • Viridi pyxidium moench
  • Glomeraria viridis Cav
  • Amaranthus ascendens Loisel
  • Euxolus viridis Moq.
  • Amaranthus emarginatus Salzm
  • Amaranthus gracilis Desi

III. TAXONOMICAL CLASSIFICATION[14,15]

• Kingdom : Plantae
• Order : Caryophyllales
• Family : Amaranthaceae
• Genus : Amaranthus
• Species : Viridis
• Botanical name : Amaranthus viridis L

IV. MORPHOLOGICAL CHARACTERS

It is an annual herb, erect, 10-75 (-100) cm stem, slender, branched, angular [16,17].
✓ Leaves - Dark green of upper surface and light green at lower surface.
✓ Flower - Flowers are unisexual and small with green or reddish tinge colour.
✓ Fruit - Fruits are sub globose, less than 1 mm long.
✓ Stem - The stem is light green in colour, cylindrical in shape with irritating
✓ Root - Whitish in colour, cylindrical in shape with pungent odour.

V. CHEMICAL CONSTITUENTS OF A. VIRIDIS

Amaranthus Viridis contains so many chemical constituents such as,[18,19]

➢ Quercetin
➢ Kaempferol
➢ Myricetin
➢ gallic acid.
➢ vanillic acid
➢ syringic acid
➢ p-caumaric acid
➢ ferulic acid
➢ Isoquercetin
➢ Rutin
➢ Vitexin, etc.

• These are all the chemical constituents of Amaranthus viridis which have following pharmacological activities.

VI. QUERCETIN

Quercetin is the aglycone form of a number of other flavonoid glycosides, such as rutin (also known as quercetin-3-O-rutinoside) and quercitrin, found in citrus fruit, buckwheat, Amaranthus viridis and onions [22,23,24].

Quercetin is also having the antioxidant and anti-inflammatory effects which reduce swelling, kill cancer cells, control blood sugar, and help prevent heart disease. Quercetin is most commonly used for conditions of the heart and blood vessels diseases and also to prevent cancer [25,26,27].

Mechanism of Action

Several studies in vitro using different cell lines have shown that quercetin inhibits lipopolysaccharide (LPS)-induced tumor necrosis factor α (TNF-α) production in macrophages and LPS-induced IL-8 production in lung A549 cells. [28,29,30].
Figure 3: Mechanisms of action of ABT263 and Quercetin. Schematic view of the molecular pathways targeted by the compounds. While ABT263 binds and blocks BCL2/Bcl-xL, quercetin acts by blocking diverse steps of JNK, PI3K, RAS/RAF/MEK/ERK and NF-kB pathways.

Figure 4: Flavonoids in cancer. Flavonoids exert their anti-inflammatory activities by reducing the production of reactive oxygen species (ROS) and the down-regulation of several inflammatory mediators through key inhibition of signaling pathways. NF-κB—nuclear factor-kappa B; MAPK—mitogen-activated protein kinase; STAT—signal transducers and activators of transcription.

VII. KAEMPFEROL

Kaempferol (3,4',5,7-tetrahydroxyflavone) is a natural flavonol, a type of flavonoid, found in a variety of plants and plant-derived foods including kale, beans, tea, spinach, and broccoli amaranthus viridis[31,32,33]. Kaempferol reduces the risk of chronic diseases, especially cancer.

Figure 5: Kaempferol pharmacological Property[34,35]

Cell cycle arrest and apoptosis by kaempferol

Most of these studies says that the mechanism of Kaempferol (KMF) is inhibit the proliferation of various cancer cells either via cell cycle arrest. KMF-dependent inhibition of cancer proliferation is mediated through arrest of the different phases of cell cycle and inhibition of cell cycle transition points including G0/G1 transition in esophagus squamous cell carcinoma inhibits the expression of various cyclins like cyclin D1 and cyclin E in breast cancer cells cyclin B1 in gastric cancer cells and renal cell [36,37,38]. KMF treatment has also been known to up-regulate the CDK inhibitors including p21 and p27 Furthermore, results of these studies demonstrate that KMF-dependent arrest of G0/G1 or G2/M transition is possibly due to inhibition of epidermal growth factor receptor (EGFR) activity, hexokinase-2 expression inhibition of the activity of estrogen or uptake of glucose.[39,40]

Figure 6: This figure depicts the cell cycle inhibitory effect of KMF through the regulation of various proteins molecules. KMF inhibits or reduces the expression of cyclin D/cdk 4/6, cyclin E/cdk 4/6, and cyclin B/cdc2 at G1/S and G2/M cell cycle check points. It increases the expression of p27, a member of the Kip/Cip family of CKIs which exerts negative regulation of CDK activity at G1/S phase transition. Similarly, KMF is also known to enhance the expression level of cyclin-dependent kinase inhibitor p21WAF1/Cip1 which promotes the cell cycle arrest in response to various stimuli.
Anti-angiogenesis effect of kaempferol

An order to meet their energy needs, cancer cells have a high metabolic rate, which is then linked to neovascularization (angiogenesis). Various transcriptional (ERK 1/2, Akt, and MAPK) and growth factors (VEGF and FGF) have been implicated in the cancer, according to numerous research [41,42,43]. These elements are being targeted as a therapeutic strategy for the treatment of cancer that is already advanced. When Huh7 cells are treated with KMF in hypoxic (low oxygen tension) conditions, the HIF-1 protein is inhibited through the inactivation of the p44/42 MAPK pathways, which may be a potential method of cancer inhibition. According to research utilising human ovarian cancer cells, KMF can drastically reduce angiogenesis by changing the production of VEGF through both HIF-dependent and independent mechanisms.[44,45]

Figure 7: The anti-angiogenic and anti-metastatic actions of KMF are shown in this image. It has been discovered that KMF inhibits HIF-1, which starts neovascularization in tumours when there is a lack of oxygen. Additionally, KMF attenuates the stimulation of endothelia cells caused by VEGF and its receptor VEGF FR. Additionally, KMF blocks the well-defined signalling pathway Akt/mTOR/p07S6K, which is involved in neovascularization during the growth of tumours. Additionally, it prevents the phosphorylation of STAT3 or STAT3, both of which are necessary for the activation of HIF-1 to initiate signalling cascades. KMF observes a down-regulation of inflammatory mediators such as iNOS, which stimulates the VEGF. Additionally, KMF blocks the MAPK/Akt pathways, which in turn inhibits the MMPs (MMP 2 and 9), two enzymes crucial for the remodelling of the extracellular matrix (ECM) during the progression of cancer.

p-Coumaric acid

Fruits, vegetables, and beverages contain phenolic chemicals known as hydroxycinnamic acids (HCs), which include coumaric acid, ferulic acid, sinapic acid, caffeic acid, chlorogenic acid, and rosmarinic acid (coffee, tea, wine). The chemical formula of p-coumaric acid (p-CA), sometimes called 4-hydroxycinnamic acid, is C9H8O3. Mice are not adversely affected by the phenolic acid p-CA (LD50 = 2,850 mgkg-1).

It is abundantly present in mushrooms, grains (corn, rice, oats, and wheat), fruits (apples, pears, and grapes), and vegetables (carrots, potatoes, beans, onions, and tomatoes). It has a number of biological properties, including those that are anti-inflammatory, antioxidant, anti-diabetic, anti-platelet aggregation, and anti-cancer [46,47,48]. Recent studies have demonstrated that p-CA has the capacity to limit the proliferation and migration of tumour cells. For instance, it can significantly and dose-dependently decrease the proliferation and migration of colon adenocarcinoma HT29-D4 cells and human lung cancer A549 cells. p-CA can also encourage the death of tumour cells; for instance, it prevents the growth of polyps in the rat colon by enhancing the detoxifying and apoptotic effects of 1,2-dimethylhydrazine.

The pharmacological effects of p-CA also impede the synthesis of melanin [49]. A crucial enzyme that catalyses the synthesis of melanin is tyrosinase (TYP). Tyrosine (TYP) and p-CA fight for the active site on TYP due to their comparable structural similarities. By preventing TYP activity, p-CA prevents cells from producing melanin [51]. In this study, we looked into how p-CA affected the growth of mouse melanoma B16 cells and human melanoma A375 cells. The findings shown that p-CA can stop the cell cycle and trigger apoptosis in melanoma cells to prevent them from proliferating [50].

Figure 8: P-Coumaric acid Pharmacological activity

Anti-Cancer Mechanism

Uncontrolled cell division is the root cause of a number of disorders, including cancer. Rapid self-proliferation, insensitivity to anti-proliferative signals, and evading signalling from apoptosis are just a few of the ways that cancer can arise. The mechanism of action of anti-cancer medications can be altered, for example, by changing the gene that controls cell cycle, apoptosis, or proliferation; or by inhibiting the enzymes required for cell proliferation [51]. ROS accelerate the start of tumour development and cause carcinogenesis [52,53,54]. Figure 6 shows how p-CA works to prevent cancer.
Syringic acid

A phenolic substance with a natural origin is syringic acid (SA) [55]. With its anti-oxidant, antibacterial, anti-inflammatory, and antiendotoxic properties, SA is a great drug candidate for treating a variety of illnesses, including diabetes, cardiovascular disease (CVD), cancer, cerebral ischemia, neuropathy, and liver damage. The physiological features of syringic acid include hepatoprotective, anti-inflammatory, anti-mitogenic, antioxidant, anti-cancer, and anti-diabetic effects [56].

Ferulic acid

Ferulic acid has demonstrated antineoplastic efficacy in a variety of malignancies, including colon and lung cancer and tumours of the central nervous system. It was extracted from the leaf of Amaranthus viridis, a perennial herb. However, its possible function in preventing the spread of breast cancer is yet unclear [57]. New therapeutic approaches are urgently required since metastatic disease, which frequently affects breast cancer patients, is the main cause of mortality. Antineoplastic activity in a variety of cancers, including colon and lung cancer and tumours of the central nervous system, has been demonstrated by ferulic acid, which was extracted from Amaranthus caudatus seeds and the perennial herb Ferula foetida [58]. However, its possible function in preventing the spread of breast cancer is yet unclear [59]. In the current research, using in vitro and in vivo models based on breast cancer cell lines, we assessed the anticancer efficacy of ferulic acid. First, we demonstrated that the treatment of the breast cancer cell line MDA-MB-231 with ferulic acid reduced viability, enhanced apoptosis, and suppressed the capacity for metastatic spread. Furthermore, it was shown that reversing the epithelial-mesenchymal transition controlled ferulic acid’s anticancer efficacy and its function in preventing metastasis (EMT).
The anticancer effect of ferulic acid was further confirmed in a mouse model using an MDA-MB-231 xenograft, where a substantial decrease in tumour volume, weight, and enhanced apoptosis were seen. When considered collectively, these findings suggest that ferulic acid may be used as a potent therapeutic drug to treat breast cancer [60].

Figure 12: Therapeutic uses of ferulic acid

**VIII. CONCLUSION**

The ethano-botanical, phytochemical, and pharmacological information about *Amaranthus viridis* (L) is gathered from the previously published information. The plant has a wide range of pharmacological actions that have been reported, making it effective in treating a wide range of diseases. It was noted because it had a small number of phytoconstituents linked to a limited number of biological functions. Therefore, it is necessary to identify the other phytoconstituents that can be employed as lead compounds to create innovative drugs with potent therapeutic effects. It is crucial to isolate and characterise phytoconstituents, to understand the mechanism of action of isolated compounds, and to conduct clinical trials on substances. The importance of medicinal plants in basic healthcare has grown in the current global environment. Consequently, the information supplied may be useful for requires additional investigation to screen the substances accountable for various bioactivities and to clarify the molecular mechanism of action.

**Acknowledgments**

The authors acknowledge all participants for their valuable time and commitment to the study.

**Competing interests**

The authors declare that there are no commercial or financial relationships that could constitute as potential conflicts of interest in the conduct of the research.

**Funding statement**

The authors declare that this study received no form of financial support from any institution.

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