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Plant Flavonoids: Novel Drug Discovery for Cancer Research

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ABSTRACT

This review brings out some medicinal plants that have therapeutic potential due to the presence of natural antioxidants. Majority of their antioxidant activity is due to bioactive compounds viz. Flavonoids and Polyphenolic compounds. The Present research reveals that Flavonoids and polyphenolic compounds activity have important effects on cancer chemoprevention and chemotherapy. Numerous mechanisms of action have been recognized, along with inactivation cancer, antiproliferation, and cell cycle arrest, stimulation of apoptosis and inhibition of angiogenesis. This work has particularly enhanced the function of antioxidants activity of Flavonoids for cancer research.

Key word: Flavonoids, Antioxidant, Free radical and Cancer research

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INTRODUCTION

A human adult comprises about 10^{15} cells; scores of them divide and differentiate in order to refurbish organs and tissues, which require cell turnover [1]. However, if the cells do not stop dividing, they may lead to cancer. Characteristically, cancer is an unrestrained proliferation of cells which become structurally abnormal and possess the ability to detach them from a tumor and establish a new tumor at a remote site within the host [2]. Globally, cancer represents a substantial burden of disease in the community and appears to be a prime cause of concern. Every year over 200,000 people are diagnosed with cancer in the United Kingdom only, and approximately 120,000 die as an aftermath of the disease [3]. According to the International Agency for Research on Cancer, in 2002, cancer killed > 6.7 million people around the world and another 10.9 million new cases were diagnosed [4]. If the results are extrapolated, at the same rate, an estimated 15 million people will have cancer, annually, by 2020. According to an estimate given by American Cancer Society [5], about 1,500,000 new cases and over 500,000 deaths are expected in the US by 2009. The National Cancer Registry of South Africa has spotted the cancers of bladder, colon, breast, cervix, lungs and melanoma commonly among inhabitants [6]. Attempts are underway to work out the therapeutic and anti-neoplastic properties of medicinal plants [7, 8, 9, 10, 11, and 12]. Plant bioactive compound is a potential source for antitumor and cytotoxic activities [13, 14]. Consequently, herbal medicines have received much attention as substitute anticancer drugs.

FLAVONOIDS

Flavonoids are polyphenolic compounds form one of the key classes of derivative metabolites; they exhibit a variety of structures and are responsible for the major characteristics properties. Flavonoid represents one of the major groups of plant phenolics and has potential quality as beneficial agents. Flavonoids are more correctly referred as anti oxidant inside this review reporting on some Medicinal plants comprises cancerous potential due to the existence of natural antioxidants implementation as reducing agents, free radical scavengers and quenchers of singlet oxygen. It is well conventional that plants have constantly been valuable sources of antitumor or cancer obstacle compounds [15, 16]. Huge groups of different phenolic compounds from plants are significant and vital anticancer agents [17, 18]. In numerous cases, they are much more successful and In fact, they are much studied in order to discover their additional use in pharmacy and medicine in the avoidance and healing of cancer. Over 4,000 flavonoids have been identified, many of which occur in fruits, vegetables and beverages (tea, coffee, beer, wine and fruit drinks).

Recent studies have demonstrated that flavonoids found in fruits and vegetables may also act as antioxidants. Like alphatocopherol, flavonoids contain chemical structural elements that may be conscientious for their antioxidant activities.

Basic Structure of Flavonoid Molecule

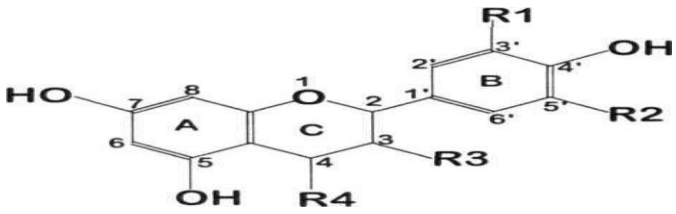

Figure.1 the Basic Flavonoid Molecule.

Different Structure of Flavonoids

Flavonoids are a group of more than 4000 polyphenolic compounds that occur in nature in foods of plant foundation. These compounds acquire a common phenyl-benzopyrone arrangement (C6-C3-C6), and are categorized according to the saturation level and opening of the fundamental pyran ring, mainly into flavones, flavanols, isoflavones, flavonols, flavanones, and flavanonols (Figure. 2).

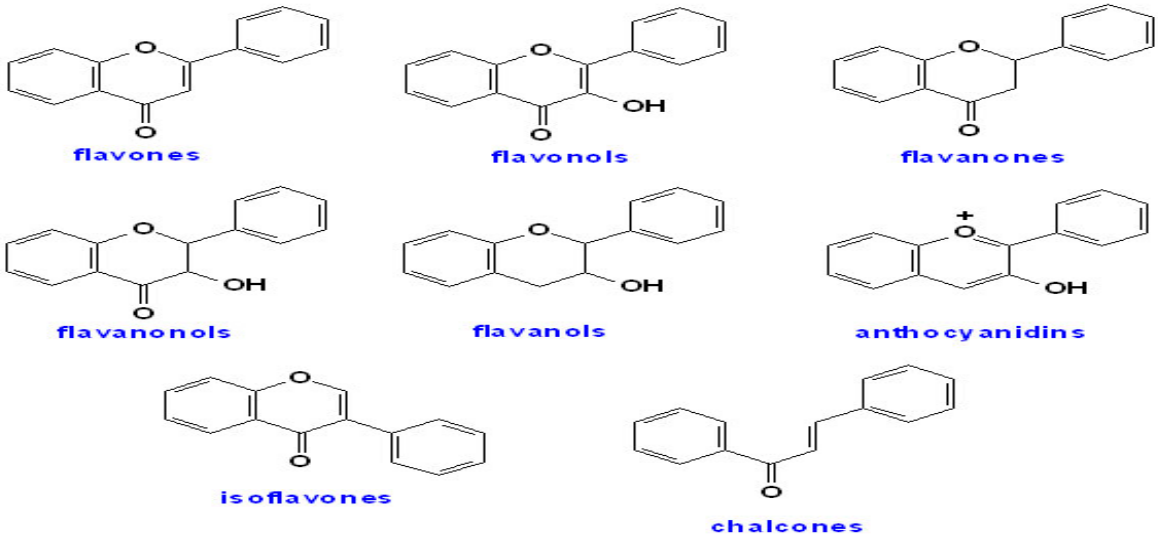

Figure .2 Different Structures of Flavonoids

WHAT ARE FREE RADICALS?

Free Radicals are molecules with an unpaired electron. Due to the presence of a free electron, these molecules are highly reactive. Free radicals and related species have attracted a great deal of attention in recent years. They are mainly derived from oxygen (reactive oxygen species/ROS). Free radicals can adversely alter lipids, proteins and DNA and have been implicated in aging and a number of human diseases. Lipids are highly prone to free radical

damage resulting in lipid peroxidation that can lead to adverse alterations. Free radical damage to protein can result in loss of enzyme activity. Damage caused to DNA, can result in mutagenesis and carcinogenesis.

Formation of Free Radicals

In general, bonds don't split to leave a molecule with an odd, unpaired electron. But when weak bonds split, free radicals are produced. Free radicals are extraordinarily unstable and act in response quickly with other compounds, when the "attacked" molecule loses its electron; it becomes a free radical itself, and initiates a chain reaction. All this happens within nanoseconds. Once the procedure is in progress, it can cascade, finally resulting in the trouble of a living cell.

Free Radical-Targets

Free radicals attack three main cellular components.

Lipids

Peroxidation of lipids in cell membranes is capable of damage cell membranes by disorderly fluidity along with permeability. Lipid peroxidation can also harmfully change the function of membrane bound proteins such as enzymes as well as receptors.

Proteins

Express damage to proteins is capable of caused by free radicals. This can influence numerous kinds of protein, interfering through enzyme goings-on and the utility of structural proteins.

DNA

Destruction of DNA caused by free radical cause violence to creation of the poly (ADP-ribose) synthesis enzyme. This splits NAD+ to aid the repair of DNA. On the other hand, if the damage is wide-ranging, NAD+ levels may be converted into depleted to the degree that the cell possibly will no longer be able to function and dies. The location of tissue injure by free radicals is dependent on the tissue and the reactive species. Far-reaching damage can show the way to death of the cells.

It is now widely held that the mutagenic capacity of free radicals is due to the direct Interaction of hydroxyl radicals (OH) with DNA. Hydroxyl radicals have been detected by electron paramagnetic spectroscopy under conditions of active oxygen induced DNA damage. Hydrogen peroxide and superoxide do not directly interact with DNA to produce oxidative lesions in-vitro [19]. However, on interaction of these free radicals with transition metals the hydroxyl radical is produced which is responsible for DNA damage. Hence, the hydroxyl radical causes DNA damage by direct interaction in the generation of many of its genetic lesions. By selectively modifying gene expression in initiated cells, tumour promoters can obtain the production of

clonally-derived benign growths. These tumours can be converted into rapidly growing malignant neoplasms through further DNA damage.

Figure .3 free radical functions

FREE RADICALS AND CANCER

Numerous research studies support the fact that many cancers, breast cancer in particular, are diet related. The development of cancer is composed of a series of complex processes of cellular and molecular changes. Active oxygen species and other free radicals have long been known to be mutagenic. There is also evidence that they act as mediators of the other phenotypic and genotypic changes that lead from mutation to neoplasia. Free radical production is universal in all respiring organisms and is enhanced by many disease processes, carcinogen exposure and under conditions of stress. Many chemical carcinogens are thought to act through the production of free radical metabolites or processes.

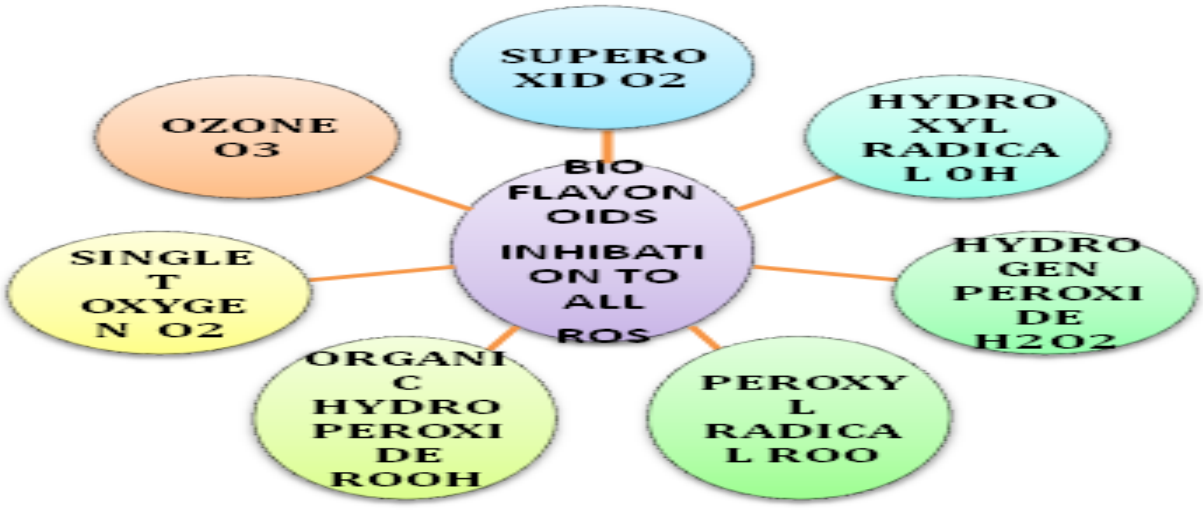

Figure. 4 bio-flavonoids inhibition to all ros

Flavonoids: Biologically Active Compounds

Quercetin is the major bioflavonoid in the human diet. In recent years, research about quercetin has ranged from considering it potentially carcinogenic to examination of its promise as an anti-cancer agent. Progressively more; flavonoids are becoming the area under discussion of therapeutic research. Among the numerous products identified from medicinal plants, flavonoids represent one of the most interesting groups of biologically active compounds. These bio-flavonoids and polyphenolic compounds flaunt an amazing variety of biological activity lying on cancer avoidance. These comprise, for instance, antiallergic, anti-inflammatory, antioxidant, antimutagenic, and anti-carcinogenic, activities.[20, 21–22] of the majority flavonoids have been confirmed to inhibit proliferation in many kinds of cultured human cancer cell lines, while less or no toxic to human typical cells.[23, 24, 25, 26, and 27]. Flavonoids are also helpful at inhibiting signal transduction enzymes, for instance, protein tyrosine kinase (PTK), [28,29] protein kinase C (PKC), [30] and phosphoinositide 3-kinases (PIP3), [31,32] which are concerned in the regulation of cell proliferation and considerable anticancer properties observed of flavonoids may be due to blunt apoptosis. [33, 34, 24, 25,35,36,37]. Flavonoids have been shown as angiogenesis inhibitors derived from natural sources.[38] Therefore, these compounds may have potential for the treatment of solid tumors.[39, 40]

Flavonoids and Cancer Prevention

Dietary agents identified from fruits and vegetables contribute to keeping balanced cell proliferation and preventing cell carcinogenesis. Dietary flavonoids, combined with other components such as various vitamins, play an important role in cancer prevention. Major flavonoids have specific active ingredient(s) with cancer therapeutic effects. Flavonoids act on reactive oxygen species, cell signal transduction pathways related to cellular proliferation, apoptosis, and angiogenesis. Quercetin and apigenin inhibited melanoma growth and influenced the invasive and metastatic potential in mice. This finding may offer new insights about possible therapies for metastatic disease. It has been stated that flavonoids, as antioxidants, can inhibit carcinogenesis. [41] Some flavonoids- such as fisetin, apigenin, and luteolin are stated to be potent inhibitors of cell proliferation.[42] However there have been a number of reports that directly contradict the potential role of flavonoids as antioxidants/anticancer agents. Previously published relevant literature for protection against some forms of cancer have shown many common flavonoids such as the synthetic flavone, flavopiridol, soy isoflavonoid- Genistein, or the common dietary flavonol-quercetin to be emerging as prospective anticancer drugs and some of them have already entered clinical trials. And now a day's many researchers have tried to

elucidate possible structural activity relationships that might lead to new drug discovery and insights on the biological effects of the main flavonoids, as well as the epidemiologic evidence that support their potential cancer protective properties. Overall, exciting data show that dietary flavonoids could be considered as a useful cancer preventive and conventional approach.

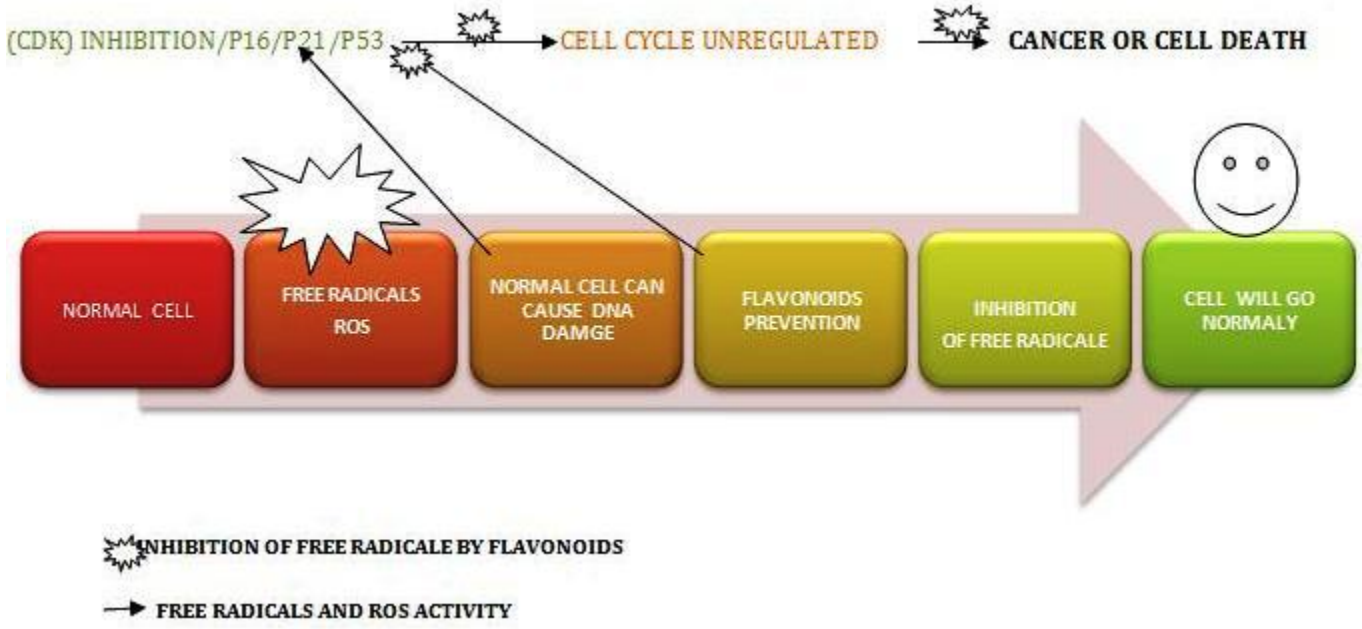

Figure .5 Free Radical and Flavonoids Their Function for Cell Death

DRUG DEVELOPMENT AND DISCOVERY

Current research reveals the different potential applications of antioxidant/free radical manipulations in prevention or control of disease. Natural products from dietary components such as Indian spices and medicinal plants are known to possess antioxidant activity. Recently more than 100 new active compounds have been isolated for clinical improvement, predominantly as anti-cancer agents from plant source. Drug development is an essential part of research owing to low bioavailability of flavonoids which has been attributed to lack of stability, excessive metabolism, permeability problems, lack of site specificity in distribution, rapid elimination etc. The scope of the review is to assess and put into perspectives salient features of some of the recently reported work on dietary flavonoids including the methylated compounds that showed improved drug-like properties in context with the required features for the lead optimization program rendering a clinical candidate. Relevance of chemistry and biological techniques can surely create novel compounds that can be opportunely produced with the help of plants. Now days a number of approaches are being considered to selecting higher plants as reference for anti cancer drug development with the aim of drug accomplishment. With this we would be able to highlight the role of conventional medicine (ethno medicine) and its value for

drug discovery. In the present time herbal products are considered to be symbols of protection in comparison to the synthetic product that are regarded as unsafe to human life and environment.

CONCLUSION

Although a large number of synthetic drugs are being added to the world of modern pharmacopoeia, but still there is no system of medicine in the world which can solve all the health problems. Several diseases like AIDS, BIRD-FLUE, and CANCER etc. still exist a great threat to the survival of humanity which must get proper to attention to evade reasonable solutions. Therefore the search for new therapeutic constituents from plants is genuine and urgent. In India, there is an ocean of knowledge about medicinal plants and rich medicinal flora, but still only a few pearls have been searched as therapeutic agents. There are large numbers of indigenous plants left which have not been investigated thoroughly from modern scientific view or their curative values have not been recognized. Thus there is an urgent need for systematic phytochemical investigation of those plants which have not been investigated systematically or worked at a time when modern facilities were not available for their potential therapeutic components.

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