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Review Article

A REVIEW: IMMUNOLOGICAL POTENTIAL OF BIOACTIVE FLAVONOIDS AND FLAVONOID CONTAINING FRACTIONS ISOLATED FROM MEDICINAL PLANTS

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ABSTRACT
Researchers have shown that flavonoids which are secondary metabolites found in plants possess several health promoting properties. Such properties include antioxidant, anti-inflammatory etc. Flavonoids have also been shown to accelerate phagocytosis, suppress both cellular and humoral responses and also inhibit the immunological memory after antigenic stimulation. They also possess inhibitory effects against certain enzymes such as protein kinase C, protein tyrosine kinases, phospholipase A_2 and others. Not much has been done concerning its immunological properties. The aim of this review work is to highlight the importance of flavonoids in the area of immunotherapy and to sensitize researchers in the implications of flavonoids in the development of new drugs that will have less side effects and low to no toxicity. It is believed that structural rearrangement and introduction of other structural components into the flavonoid skeleton could lead to the development of new drugs that could be effective in the treatment of immunological disorders.

Keywords: *Flavonoids, Immune System, Plants, Extracts*

INTRODUCTION
The immune system is responsible for the removal or destruction of pathogens such as bacteria, viruses, parasites and other extraneous substances that gain entrance into an organism and malignant and auto reactive cells within the body (Benmebarek *et al.,* 2014). Once the immune system recognizes the presence of any pathogen or extraneous matter it initiates a reaction that will be able to eliminate the foreign matter thereby combating infections and protecting the body from disease. Its integrity and efficiency are important since it is the maintenance authority of the organism. The innate immune system consists of cellular components, soluble factors, physical barriers and reticuloendothelial system. It works in unison with the adaptive immune system which produces a specific reaction and immunologic memory to each pathogen. The adaptive system comprise of soluble factors and cellular components (Goldsby *et al.,* 2000). Both innate and acquired immunity are extremely important for the maintenance of good health. A small defect in innate as well as acquired immunity can lead to serious health problems. Diseases such as arthritis, colitis, asthma, allergy, cancer and various infectious diseases are attributed to immune system dysfunction (Patwardhan *et al.,* 1990). The extent of immunosuppression in the body system determines the degree to which a patient will be susceptible to these diseases and infections. The macrophages and monocytes are the phagocytic cells that destroy any invading organism by phagocytosis. They are responsible for the initiation of immune response. These cells could pick up antigens, partially digest them and place them on cell surface so that they can interact with the T receptor thereby initiating an immune response. The T and B lymphocytes are important cells that are needed in immune response. The reduction in number and phagocytic function of neutrophils and macrophages are responsible for the suppression of the immune system of the body. Also, the deterioration of the intercellular bacteriocidal ability of cells could lead to suppressed immunity (Rao *et al.,* 1994), thus, modulation of immune response to prevent infection and treat diseases is very important.
Plants are referred to as nature's pharmacy store. They have the capacity to produce compounds called primary and secondary metabolites. These compounds can be located in the leaves, fruits, flowers, twigs, stem and root bark. Secondary metabolites found in plants have been reported to possess some beneficial

effects that can alleviate sicknesses and diseases. Different plant parts have been used by traditional health practitioners for the modulation of human body's defense mechanisms (Pezzuto, 1997; Crag, 1999). A large number of medicinal plant extracts and isolates have been reported to exhibit immunomodulatory effects. Some of such plants include *Viscum album*, *Panax ginseng*, *Asparagus racemosus*, *Azadirachta indica*, *Tinospora cordifolia*, *Polygala senega*, *Ocimum santum* (SaiTam *et al.*, 1997; Estrada *et al*., 2000; Mediratta *et al*., 2002), *Achillia talagonica*, *Plantago ovate*, *Boerhaavia diffusa*, *Stachys obtsicrena*, *Pollen Typhae* and silymarin. Most medicinal plants contain the secondary metabolite known as flavonoids (Figure 1). The flavonoids are made up of two aromatic rings called rings A and B and one heterocyclic ring called ring C or an open chain of three carbon atoms. The flavonoids are classified based on the C ring, degree of unsaturation and oxidation of the C-ring. When the classification is based on the C ring, Isoflavones are obtained if the B ring is attached at position 3 on the C ring while neoflavonoids are obtained if the B ring is attached at position 4 on the C ring. Other classes of flavonoids are obtained when the B ring is attached at position 2 on the C ring. The compounds include flavones, flavonol, flavanones, flavanonols, flavanols, catechins and anthocyanins. Those flavonoids with open C ring are referred to as chalcones (Figure 1). Treatment of immunological disorders with synthetic drugs is fast losing ground due to its associated side effects and high cost. The aim of this review work is to highlight those flavonoids and flavonoid containing fractions that possess immunologic potentials which can serve as alternative source of drugs that can be useful in the treatment of immunological disorders.

Methodology

Materials for this review work were obtained from books and periodicals found in both private and public libraries, data banks, proceedings of scientific conferences and websites. The review work covers the period 1988 to 2015.

DISCUSSION

Immunology deals with the study of the immune system of living organisms; the physical, chemical and physiological characteristics of components of the immune system in-vitro, in-vivo and in-situ (Benmebarek *et al.,* 2014). It also involves the relationship between the body systems, pathogens and immunity.

Immunomodulation and immunosuppression are used to correct defective immune system. Immunomodulation is the modulation or regulation of immunity either by enhancing or by reducing the immune response. An immunomodulation can influence any part of the immune system in a specific or non specific manner. Immunostimulation occurs when the effector cells are stimulated or their metabolic inducers are produced or when the immunity limiting factors are inhibited. Immunosuppression can be achieved by stimulating the inhibitor cells and humoral factors or inhibition of effector cells (Agarwal *et al*., 1997). Since the ethiological and pathophysiological modes of action of diseases are entwined with the immune system of the body, modulation of the immune system towards the alleviation of diseases is important and has been of interest for years. There is great concern on the effect of allergies and autoimmune diseases on humans, coupled with transplant rejection. This has led to the synthesis of immunosuppression drugs that can suppress these unwanted immune responses. Despite the fact that these synthetic drugs are effective, they also have the tendency to induce side effects such as nephrotoxicity, hepatotoxicity and induction of diabetes, hypertension and neurotoxicity.

Over the past decade, scientists have shown interest in the health benefits of flavonoids and flavonoid containing fractions. Several researchers have reported on beneficial effects of flavonoids such as antimicrobial (Bojase *et al.,* 2002; Dastidar *et al.,* 2005), anti-inflammatory (Elango *et al.,* 2012), antioxidant (Chacha *et al.,* 2005), etc. Certain flavonoids isolated from plants have been reported to possess immunological effects. For example, quercetin (Figure 2) inhibited antigen presentation in macrophages, lymphocyte motogenesis stimulated by phytomitogens such as phytohemaglutinin and concanaralin A, which indicates that they can have profound effect on cell-cell interactions. Huang *et al.,* (2010) reported that quercetin possess potent immunosuppressive activity and therefore, could be used in

the prevention and therapy of chronic inflammatory, autoimmunity and transplantation deactivating dendritic cells and function. The dendritic cells play important role in linking innate and adaptive immunity. Thus, dendritic cells are regarded as major targets of immunosuppressants for the control of harmful immune responses. The immunomodulatory effects of quercetin on NK cell (Yu *et al*., 2010), macrophages (Kim *et al*., 2005), mast cells (Min *et al*., 2007), neutrophils (Morcira *et al*., 2007), B cells (Gong and Chen, 2003) and T cells (Yu *et al*., 2008) have been reported. Genistein (an isoflavone) (Figure 2) inhibit the B cell antigen receptor which causes B cell activation with accompanying phosphorylation of tyrosine residues in several proteins within the B cell. Inositol kinase can be inhibited by the isoflavone orobol (Figure 2), quercetin and fisetin (Figure 2) while the isoflavonone psi-tectorigerin (Figure 2) inhibits the epidermal growth factor induced by phosphatidyl turnover in epidermal carcinoma cells (A 231 cells). It was observed that the flavonoid plantagoside (a flavonone glucoside) (Figure 2) could inhibit mouse spleen cell antibody response to antigens.

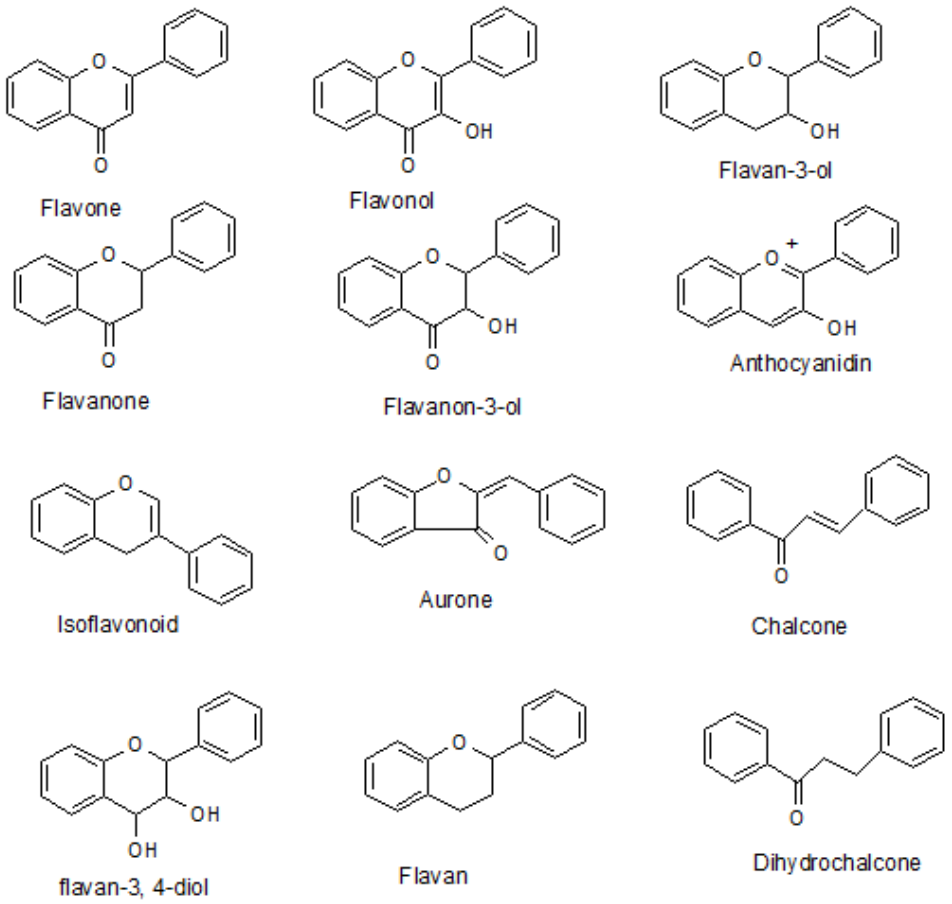

Figure 1: Classes of Flavonoids

Flavonoids are known to affect proliferation, differentiation and apoptosis in cancer cells and may play an important role in cancer chemoprevention. They may enhance anticancer efficacy of chemotherapeutics and reduce cytotoxicity to immunocompetent cells. Pretreatment with flavonoids both in-vitro and in-vivo sensitizes cancer cell to growth inhibition and apoptosis induced by chemotherapeutic agents. It is likely that flavonoids by inhibition of P-gp activity increase the accumulation of chemotherapeutic in P-gp expressing cancer cells which result in alteration of absorption and bioavailability of these drugs after

coadministration of flavonoids with cytostatic drug. Therefore, polyphenolics such as flavonoids may serve as potent adjunct to chemotherapy in the treatment of cancers (Nada and Ivan, 2008).

Flavonoid containing fractions or extracts have been reported to exhibit immunomodulatory properties (Chen *et al*., 2005). Sudarsono and Nugroho, (2014) examined the efficacy of ethyl acetate fraction of *Ficus septic* Burm. f. on lymphocyte proliferation and macrophage phagocytosis activity and noted that it possess immunomodulatory effect. The in-vivo immunomodulatory potential of *S. ocymastrum* on macrophage phagocytosis was evaluated by Benmebarek *et al*., (2014). Their results showed that the extract of the plant exhibited immunostimulatory effect at low concentrations while immunosuppressive activity was observed at higher concentrations. According to Tao *et al*., (2014) phagocytic function of macrophages improved greatly with propolis flavonoid liposome. It also aided in the release of IL-1β, IL-6 and IFN-γ. They concluded that propolis flavonoids liposome could serve as a potential adjuvant due to its immune modulatory activity. The immunoregulatory effect of *Vitis vinifera* was investigated by Lui *et al*., (2011). They noted that the fruit extract exhibited immunoregulatory effect due to the presence of flavonoids in the fruits. According to Percival and Sims, (2000) moderate intake of red wine could augment the immune response of the body towards different types of sicknesses. This effect is attributed to the presence of polyphenols in the red wine; but Watzel *et al*., (2004) had a contrary view. They put forward that the consumption of red wine had no effect on human immune cell function. Also, that polyphenol rich beverages do not suppress immune responses in humans. The study of the ethyl acetate extract of *Caesalpinia pulcherrima* revealed that it has immunomodulatory property on human neutrophils. This activity could be due to the presence of the flavonoid, 2´-hydroxy-2, 3, 4´, 6´-tetramethoxy chalcone (Madagundi *et al*., 2012). Finlay *et al*., (1988) reported that Flavone acetic acid enhance natural killer and lymphokine- activated killer cell activity in mice by effecting modulation while Triozzi *et al*., (1990) suggested that it does not enhance immunological responses in humans. The flavonoids of *Oldenlendia diffusa* could prevent acute ulcerative colitis in mice. It was proposed that its mechanism is related to the inhibition of NF-κB p65 activation, reduction of IL-8, TNF-α expressions and increase in the anti-inflammatory factor IL-10 (Luo *et al*., 2014). The aqueous extract of *Achillea wilhelmsii* was evaluated for its immunomodulatory effect on mice. It was observed that the aqueous extract exhibited immunostimulatory effect on both humoral and cellular immune functions in mice (Sharififar *et al*., 2009). Zalizar, (2013) reported that flavonoids isolated from *P. niruri* exhibited immunostimulatory properties. They can increase phagocytic capacity and antibody titre levels. Flavonoids have siginificant in-vivo effects on homostatis within the immune system. It was noted by Middleton and Kandaswami, (1992) that certain flavonoids can affect gene expression, elaboration and effects of cytokine receptors. It was suggested that the cell functions are regulated by the stimulation of inhibition of protein phorsphorylation by flavonoids. Kim and Cho (1991) studied the structure activity relationships of flavonoids in immunosuppression. Their results showed that the flavonoids studied could significantly accelerate phagocytosis and suppress humoral, cellular immune response and the development of immunological memory after the antigenic stimulation. Among the studied flavonoids malvin (Figure 2) was the most active in phagocytosis while disodium chromaglycate and morin (Figure 2) were the most active in humoral and cellular immunosuppression. Daizein (Figure 2) had the highest inhibitory potency activity in the development of memory cells. It was noted that the C2-3 double bond and C4 ketone group in the C-ring are necessary for immunosuppression to occur. The same activity was observed for flavonoids with substitution with benzene at positions 2 and on the C-ring. Flavonoids that possess open C-ring also exhibited immunosuppression. Glycosylation at position 3 on the C-ring produced reduced immunosuppressivity. It was also noted that increasing the hydroxylation of the B-ring increased the potency than that of monohydroxylation. Chromanochromanone also exhibited immunosuppessive activity. Examination of the effect of (-) - epicatechin (Figure 2) and cocoa extract on the activation of a lymphoid cell showed that it significantly reduce IL-2 rahpa expression on activated cells, inhibited IL-2 secretion in a dose dependent manner while IL-4 was enhanced up to 4.5 fold. It was also noted that cocoa extract down-modulated T lymphocyte activation thereby affecting the acquired immune response (Ramiro *et al*., 2005). In the study of the immunological properties of parsley on phyto

hemaglutinin-stimulated splenocytes (T cell) and lipopolysaccharide-stimulated B cells in adaptive immune system, it was observed that parsley essential oil exhibited immunosuppression activity on the proliferation of phytohemaglutinin stimulated splenocytes at all concentration while that of unstimulated and LPS-stimulated splenocytes occurred at lower doses. The production of NO by stimulated and unstimulated macrophages was significantly reduced. The immunological effects of parsley are due to its inhibitory effects on PHA-stimulated splenocytes which is as a result of the production of cytokines such as IFN-γ and IL-2 which are vital for T-cell proliferation. They noted that parsley essential oil modulate the activity of macrophages without any cytotoxic effect (Karimi *et al*., 2012). Examination of the effects of quercetin, taxifolin, nobiletin and tangeretin (Figure 2) on the in-vitro growth of a human squamous cell carcinoma cell line (HTB 43) showed that quercetin and taxifolin did not exhibit any inhibition at the concentrations tested while nobiletin and tangeretin exhibited a significant inhibition of the cell growth. These compounds are different from each other in their level of methoxylation (Kandaswami *et al.*, 1994). A plant extract, Padma 28 exhibited immunomodulatory effects which is associated with a shift from Th 1 to Th 2 immune response. It may also possess protective properties against autoimmune diabetes. Padma 28 is a herbal preparation from Switzerland. Type I diabetes mellitus is an autoimmune disorder. The destruction of the pancreatic beta-islets results in insulin deficiency and hyper glycemia (Weiss *et al.*, 2011).

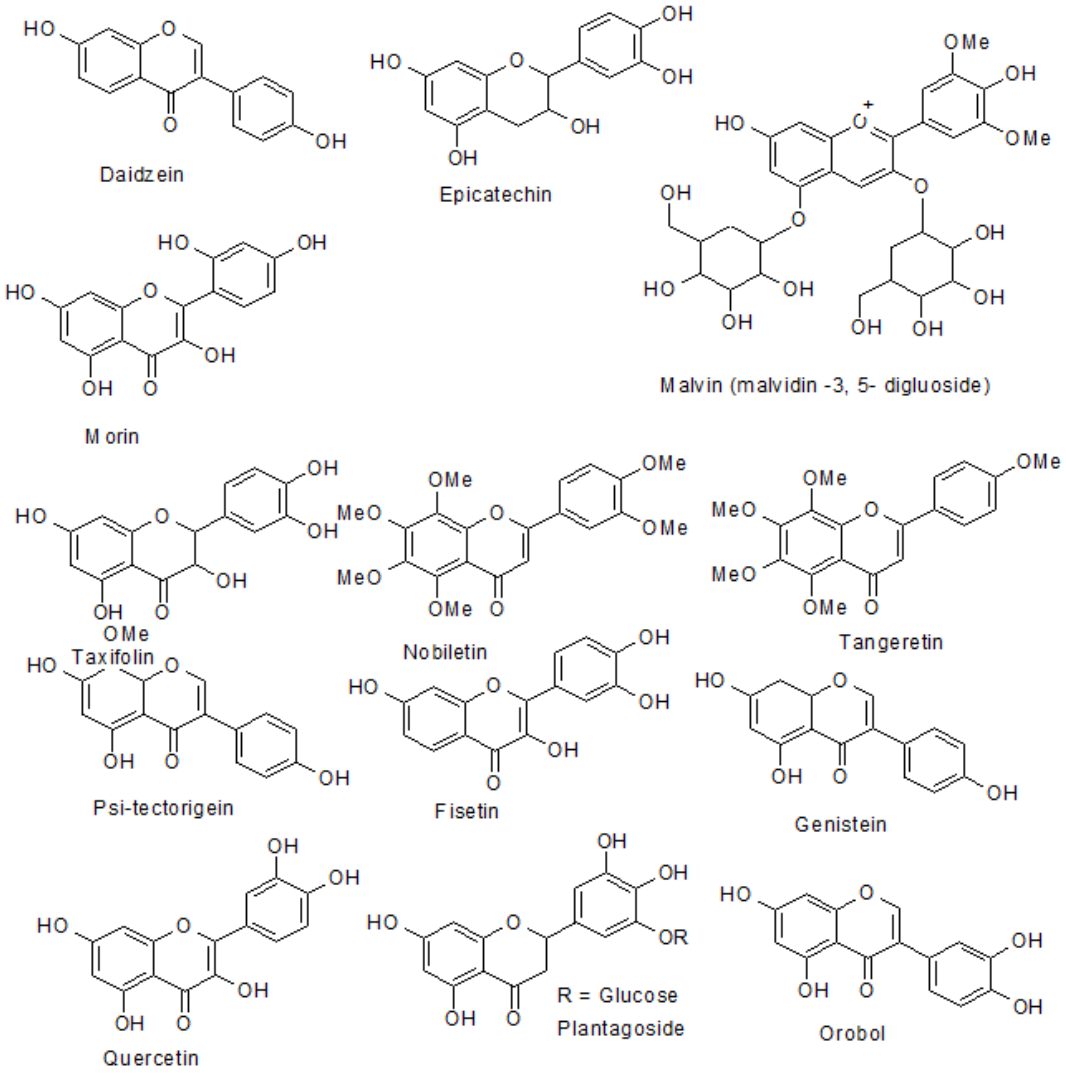

Figure 2: Examples of Flavonoids with Immunological Effects

Conclusion

Immunological disorders have been managed with the use of synthetic drugs; but the use of these drugs has resulted in side effects which are equally deleterious to the patient's health. Therefore, there is the need to find alternative source of drugs that can be effective and possess little or no side effects. This has lead researchers to investigate plants; and flavonoids which are a wide range of secondary metabolites found in plants have been reported to possess immunological properties. It is believed that modification of the bioactive flavonoids via synthesis, coupled with all the necessary test and trial runs can lead to the production of new drugs that can combat immunological disorders.

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