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Review

Influence of membrane lipid composition on flavonoid–membrane interactions: Implications on their biological activity

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ABSTRACT

The membrane interactions and localization of flavonoids play a vital role in altering membrane-mediated cell signaling cascades as well as influence the pharmacological activities such as anti-tumour, anti-microbial and anti-oxidant properties of flavonoids. Various techniques have been used to investigate the membrane interaction of flavonoids. These include partition coefficient, fluorescence anisotropy, differential scanning calorimetry, NMR spectroscopy, electrophysiological methods and molecular dynamics simulations. Each technique will provide specific information about either alteration of membrane fluidity or localization of flavonoids within the lipid bilayer. Apart from the diverse techniques employed, the concentrations of flavonoids and lipid membrane composition employed in various studies reported in literature also are different and together these variables contribute to diverse findings that sometimes contradict each other. This review highlights different techniques employed to investigate the membrane interaction of flavonoids with special emphasis on erythrocyte model membrane systems and their significance in understanding the nature and extent of flavonoid–membrane interactions. We also attempt to correlate the membrane localization and alteration in membrane fluidity with the biological activities of flavonoids such as anti-oxidant, anti-cancer and anti-microbial properties.

Contents

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1. Introduction

Flavonoids are a group of polyphenols ubiquitously distributed in vegetables, fruits, seeds, roots and stem either in the aglycone form or as glycone derivatives [1]. All flavonoids possess a typical structure comprising three cyclic carbon rings denoted as A, B and C. The substitutions in the 'C' ring are used to distinguish different flavonoid subgroups [1,2]. Flavonoids possess numerous pharmacological activities such as anti-cancer, anti-diabetic, anti-atherosclerotic, anti-oxidant, anti-inflammatory properties, etc [1,2]. They are also consumed as food supplements. The pharmacological activities of flavonoids have been primarily attributed to their ability to alter the membrane-mediated signaling pathways resulting in modification of cell membrane permeability and also to their binding with specific protein targets [3]. Fig. 1 shows the structure of flavonoids and their major subgroups.

It has now been recognized that plant-derived drugs have different molecular targets in the cells that include the cell membrane, intracellular compartments and DNA [4–6]. The gateway for any molecule to enter into the cell is the plasma membrane and hence membrane interactions of a molecule will have a major influence on their mechanisms of action [3,7–12]. Consequently, the biological activities of a molecule will be a manifestation of its mode of interaction with the membrane components as well as its localization and residence time in the cell membrane. As the lipid bilayer construct is a universal component of all membranes, interactions of molecules with the membrane lipid components can be termed as 'non-specific' interactions. Such interactions can also alter the functions of the membrane-associated proteins [13]. The membrane permeation of a molecule is chiefly associated with the nature and extent of its interaction with cellular membranes [8,14]. In the case of flavonoids, the mode of membrane interaction has been mainly attributed to their lipophilicity and planar structure [15]. The number and position of hydroxyl groups influences the relative hydrophobicity of different flavonoids [3,16,17]. The presence of a 2,3 double bond in the B ring and absence of glycosidic substituent in the flavonoid structure tends to render it more planar [1]. Thus, it is evident that a strong correlation exists between the structure and biological activity of a flavonoid.

Another major parameter that can influence the biological activity of flavonoids is the fluidity of the membrane. Plasma membrane offers a diffusion barrier that protects the cell cytoplasmic contents from adverse interactions of molecules. However, it transforms into a highly permeable structure when subjected to oxidative stress leading to cell dysfunction and death [13,18]. Oxidative stress-induced membrane damage due to lipid peroxidation has been implicated in various free radical-mediated diseases such as neuronal degeneration, atherosclerosis, cancer, rheumatoid arthritis, etc., all of which are associated with altered membrane fluidity [19]. Apart from free radicals, different exogenous compounds are also known to cause similar changes in the packing density of the membrane lipids on interaction with the plasma membrane [20]. Flavonoids have been reported to localize either in the hydrophobic core of the lipid bilayer or at the membrane interface leading to corresponding alterations in the membrane fluidity or rigidity [3,7,8]. The alteration of membrane fluidity by flavonoids can significantly influence the membrane-mediated cell signaling pathways. Thus, the structure of the flavonoids as well as their ability to alter the membrane fluidity are both important factors that influence the nature and magnitude of their biological activity. This review attempts to elaborate the mode of membrane interaction of flavonoids and their biological importance with respect to lipid composition and types of membranes. This will pave a way for understanding the pharmacological importance of membrane-mediated signaling cascades for developing novel therapeutic agents.

A scan of literature reveals that though the importance of flavonoid–membrane interactions has been duly recognized, widely contrasting reports exist on their mode of interactions. The reasons for such conflicting reports may arise due to a combination of many factors. One of the reasons for the observed variations in the results could be the widely varying concentration of the flavonoids employed in these studies [8]. The concentration of the flavonoid could determine the magnitude of molecular stress at the membrane surface and in the interior of the bilayer that would be reflected in the observed effects of the interaction. Yet another aspect that could contribute to the conflicting reports on the effects of flavonoid–membrane interactions is the type of membrane model used for the study. The most common membrane models employed for such studies are planar lipid bilayers and liposome vesicles [21–25]. The lipid composition employed for forming the membrane models will have a pronounced effect on the nature as well as extent of flavonoid–membrane interactions apart from influencing their localization within the lipid bilayer. The most common lipids that have been employed for forming membrane mimics are dipalmitoyl phosphatidyl choline (DPPC), distearoyl phosphatidyl choline (DSPC), palmitoyl oleoyl phosphatidyl choline (POPC) and cholesterol. Fig. 2 depicts the lipid membranes formed using these lipids.

A distinct feature in these membrane bilayers is the difference in their lipid-packing factor. Membranes formed from DPPC or DSPC are more compactly organized with fewer packing defects due to the strong hydrophobic associative forces that exist between the saturated fatty acyl chains of DPPC or DSPC. In contrast, membranes formed using phospholipids containing unsaturated acyl chains such as POPC possess larger number of packing defects due to the *cis* double bond in the unsaturated acyl chain that prevents close association of the neighboring acyl chains [26]. Such membranes are more fluid than those formed from DPPC or DSPC. Introduction of cholesterol in the membrane tends to rigidify it because of the presence of stiffer phenanthrene rings [26]. However, increasing the cholesterol content beyond a certain limit has been found to impart greater fluidity to the membrane bilayer. This has been attributed to the mismatch in the chain length of the phospholipid acyl chains and the cholesterol structure [27]. As a result, more voids are created in the bilayer, thereby transforming it into a highly permeable structure.

The cell membrane consists of different types of lipids along with proteins. The distribution and composition of the lipids depends upon the cell type. Among the different membrane lipids, phosphatidylethanolamine (PE), phosphatidylcholine (PC) and

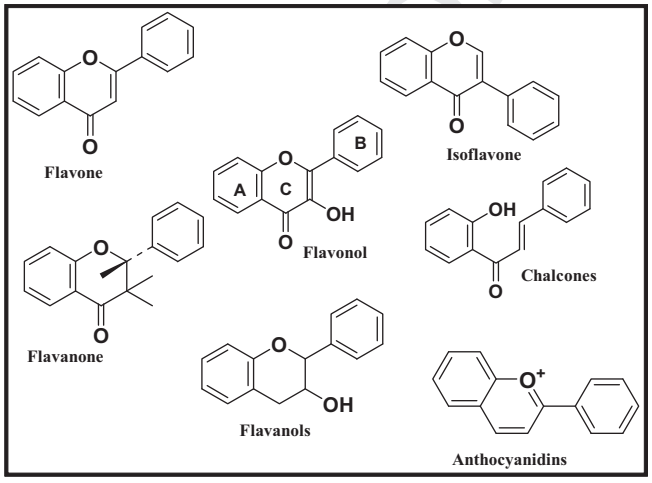

Fig. 1. Structure of flavonoids and their major subgroups predominantly present in the plant kingdom.

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