Beneficial Action of \textit{Citrus} Flavanoids on Multiple Cancer-Related Biological Pathways

O. Benavente-García\textsuperscript{1}, J. Castillo\textsuperscript{1}, M. Alcaraz\textsuperscript{2}, V. Vicente\textsuperscript{2}, J.A. Del Río\textsuperscript{3} and A. Ortuño\textsuperscript{3}\textsuperscript{*}

\textsuperscript{1}Research and Development Department of Furfural Español S.A., Camino Viejo de Pliego s/n, 80320, Murcia, Spain; \textsuperscript{2}Radiology and Physical Medicine Department, Faculty of Medicine, University of Murcia, 30100 Espinardo, Murcia, Spain; \textsuperscript{3}Plant Biology Department, Faculty of Biology, University of Murcia, 30100, Espinardo, Murcia, Spain

\textbf{ABSTRACT:} Attempts to control cancer involve a variety of means, including the use of suppressing, blocking and transforming agents. Suppressing agents prevent the formation of new cancers from pro-carcinogens, blocking agents prevent carcinogenic compounds from reaching critical initiation sites, while transformation agents act to facilitate the metabolism of carcinogenic components into less toxic materials or to prevent their biological actions. Flavonoids can act as all three types of agent.

Epidemiological and animal studies suggest that flavonoids have a protective effect against cardiovascular diseases and some types of cancer. Although flavonoids have been studied for about 50 years, the cellular mechanisms involved in their biological action are still not completely understood. In recent years, experimental studies have provided growing evidence supporting the beneficial action of flavonoids on multiple cancer-related biological pathways (carcinogen bio-activation, cell-signaling, cell cycle regulation, angiogenesis and inflammation).

Within the last decade, reports on flavonoid activity have largely associated with enzyme inhibition and anti-proliferative activity. Many of these studies have pointed to a structural-functional relationship, in that the antioxidant, enzyme-inhibition or antiproliferative activities of flavonoids are dependent on particular structural motifs. Our own studies have shown that structural factors would explain the antioxidant, antiproliferative and antimetastatic properties of some citrus flavonoids.

In this paper we discuss the relation between each structural factor and the anticancer activity of \textit{Citrus} flavonoids.

\textbf{Keywords:} Flavonoid, \textit{citrus}, cancer, apigenin, tangeretin, rutin, diosmin.

\section*{INTRODUCTION}

Flavonoids are part of a family of naturally occurring polyphenolic compounds characterized by a common benzo-\(\gamma\)-pyrone structure. They are one of the most important compounds present in vegetables, especially in genus \textit{Citrus} (family Rutaceae) \cite{1}. More than 8000 compounds with a flavonoid structure have been identified. This large number arising from the various combinations of multiple hydroxyl, methoxyl and \(O\)-glycoside group substituents on the basic benzo-\(\gamma\)-pyrone \((C_{6}-C_{3}-C_{6})\) \cite{2}.

Four types of flavonoids (flavanones, flavones, flavonols and anthocyanins, the last only in blood oranges) occur in \textit{Citrus}. In this genus flavanones are accumulated in greater quantity than flavones. The concentration of these compounds depends on the age of the plant, and the highest levels are detected in tissues showing pronounced cell divisions \cite{3-13}. These compounds not only play an important physiological and ecological role but are also of commercial interest because of their multitude of applications in the food and pharmaceutical industries \cite{1, 14-22}. This last aspect will be fully discussed below.

Cancer may be controlled by a variety of means, including suppression, blockage and transformation. Suppressing agents prevent the formation of new cancers from pro-carcinogens, blocking agents prevent carcinogenic compounds from reaching critical initiation sites, and transformation agents act to facilitate the metabolism of carcinogenic components into less toxic materials or to prevent their biological actions. Flavonoids can act in all three ways \cite{23}.

Epidemiological and animal studies point to a possible protective effect of flavonoids against cardiovascular diseases and some types of cancer. Although flavonoids have been studied for about 50 years, the cellular mechanisms involved in their biological action are still not completely known \cite{24}. In recent years, experimental studies have provided growing evidence to support the beneficial action of flavonoids on multiple cancer-related biological pathways (carcinogen bio-activation, cell-signaling, cell cycle regulation, angiogenesis and inflammation) \cite{25}.

Flavonoids may act in the different development stages of malignant tumors by protecting DNA against oxidative damage, inactivating carcinogens, inhibiting the expression of the mutagenic genes and enzymes responsible for activating procarcinogenic substances, and by activating the systems responsible for xenobiotic detoxification \cite{26}. \textit{In vitro}, flavonoids have demonstrated their capacity to modify the activity of enzymatic systems in mammals (kinases, phospholipases, ATPase, lipooxygenases, cyclooxygenases, phosphodiesterases, etc), a correlation having been observed in some cases between the flavonoid structure and its enzymatic activity \cite{1, 27, 28}.

Within the last decade, reports on flavonoid activities have been largely associated with enzyme inhibition and anti-proliferative activity. Many of these studies have shown a structural-functional relationship, demonstrating that antioxidant, enzyme-inhibition or antiproliferative activities of flavonoids are dependent on particular structural motifs \cite{29-33}. Our own studies have shown that structural factors would explain the antioxidant, antiproliferative and antimetastatic properties of some citrus flavonoids \cite{27, 28, 34-36}.

Important structural factors that may condition flavonoid activity are structure oxidation stage (flavanone, flavone ...), substituents (position, number and nature of groups in both A and B ring of the flavonoid skeleton), and the presence of glycosylation \cite{1, 31, 36}.

In this paper, we discuss the relation between each structural factor and the associated anticancer activity of flavonoids in several cancerous cell lines.

\section*{ANTIPROLIFERATIVE EFFECTS}

Although most flavonoids appear to be non-toxic to humans and animals, they have been demonstrated to inhibit proliferation in many kinds of cancerous cell lines. It has been reported that \textit{Citrus} flavonoids (tangeretin, nobiletin, quercetin and taxifolin) \cite{37} have antiproliferative effects on squamous cell carcinoma HTB43. Quercetin at 10 \(\mu\text{M}\) has demonstrated its antiproliferative activity against meningioma cells \cite{38} and against colon cancer cells, Caco-2 and HT-29 with a dose-dependent effect \cite{39}. Diosmin, another