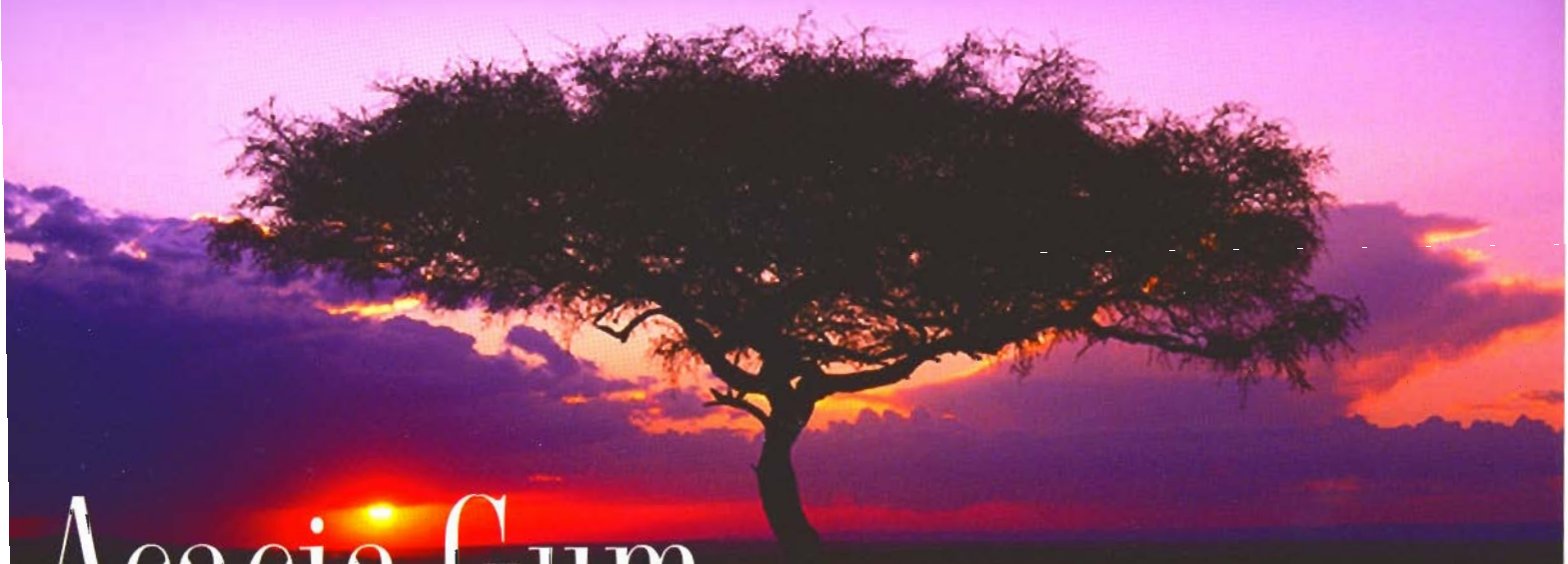
ISSN 1722-6996 AIHTEI

Agro FOOD industry hi-tech

nno 16 • July/August 2005
ublished by Tekno Scienze

European Journal of Nutraceuticals & Functional Foods

Natural, Nutritional, Renewable & Available



Acacia Gum ...Nature's Gift

4

Spedizione in a.p. - 45% art. 2 comma 20/b legge 662/96 Filiale di Milano

Antiproliferative activity of several phenolic compounds against melanoma cell lines:

relationship between structure and activity

OBDULIO BENAVENTE-GARCÍA[1], J. CASTILLO[1], J. LORENTE[1], M. ALCARAZ[2], J. YÁÑEZ[3], C. MARTINEZ[3], V. VICENTE[3], J. A. LOZANO[4].

1. Research and Development Department of Nutrafur-Furfural Español S.A. Camino Viejo de Pliego s/n. 80320 Alcantarilla. Murcia. Spain.
2. Radiology and Physical Medicine Department. Faculty of Medicine. University of Murcia. 30100 Espinardo. Murcia. Spain.
3. Pathological Anatomy Department. Faculty of Medicine. University of Murcia. 30100 Espinardo. Murcia. Spain.
4. Biochemistry Department. Faculty of Medicine. University of Murcia. 30100 Espinardo. Murcia. Spain.

INTRODUCTION

Phenolic compounds constitute a group of substances that is widely present in the plant kingdom. They are found in fruits, vegetables, nuts, seeds etc., as well as tea, red wine and citrus fruit and other food sources and are consumed regularly with the human diet[1].The main classes of phenolic compounds in the diet are phenolic acids, flavonoids, lignans, stilbenes, coumarins and tannins[2]. Many epidemiological studies have suggested that there is a link between the consumption of some foods and drinks with a high phenolic content and the prevention of some diseases, particularly cancer[3-5]. Among the properties of phenolic compounds, they have been found to protect plants against oxidative damage and may have the same role in humans[6]. They have a wide range of action, which includes antitumoral, antiviral, antibacterial, cardioprotective and antimutagenic activities[1,7]. They may act in different stages of the development of malign tumours by protecting the DNA from oxidative damage. They inactivate carcinogens by inhibiting the expression of mutagenic genes; they also inactivate the enzymes charged with activating procarcinogens and activate the systems responsible for the detoxification of xenobiotics[8].

ABSTRACT

Polyphenolic compounds are widely distributed in the vegetable kingdom and are therefore consumed regularly in the human diet. Epidemiological studies suggest that foods rich in polyphenolic compounds contribute to reducing the risk of cancer. We study the possible cytotoxicity and antiproliferative effects in vitro of twelve phenolic compounds on three cell lines of melanocytes, two of melanoma (B16F10 and SK-MEL-1) and one of non-transformed melanocytes (Melan-a) and identify the possible relationship between the chemical structure of the tested compounds and their effect on cellular viability. The said phenolic compounds corresponded to eight flavonoids with varying hydroxyl and methoxyl substituents, related structurally through the oxidation state of their flavonoid skeleton, and four phenolic acids. The cytotoxic activity of all the studied compounds was modest or not apparent. The flavonoids, luteolin, tangeretin, baicalein, quercetin and myricetin, and gallic acid showed antiproliferative effects on the tested lines. Our results suggest that a correlation exists between the structural oxidation state and the position, number and nature of substituents of the polyphenolic compounds studied and their antiproliferative effects.

Melanoma is a tumour of great transcendence since it has increased alarmingly amongst the white population in the last fifty years[9], now being the fourth most common cancer in Australia and New Zealand and the tenth most common in the USA[10]. Although it represents less than 10 percent of skin cancers, it is responsible for more than 75 percent of skin cancer-related deaths[11]. Surgical intervention is the most effective treatment in its initial phases but is of little use in advanced stages, when a great variety of therapeutic measures have been tried (dacarbazine, alkylating agents, nitrosoureas, etc). However, melanoma presents one of the worst response rates to chemotherapy[12] due to resistance phenomena[13], besides the important side effects that are known. Recent years have seen a substantial increase in studies into the effects of polyphenols on melanoma[14-16].

In this study, we look at the possible cytotoxic action and antiproliferative effects of several groups of polyphenolic compounds (flavanones, flavones, flavonols and phenolic acids) that are present in multiple foods, and the relation between their structure and biological activity shown against melanoma cell lines.

MATERIAL AND METHODS

Cell cultures

We used three cell lines: B16F10 established from a mouse primary melanoma C57BL/6JB57 (from the European Collection of cell cultures, Salisbury, U.K.), SK-MEL-1 from the lymphatic metastasis of a human cutaneous melanoma (ATCC, Maryland, MD, USA) and the line of non-transformed murine melanocytes Melan-a (kindly provided by Dr. Bennet of St. George's Hospital Medical School, London). The B16F10 and SK-MEL-1 cells were cultured in EMEM and Melan-a in RPMI-160 medium. All media (Gibco, Largley, Virginia, USA) were supplemented at 10% with fetal bovine serum (Gibco) and streptomycin plus penicillin (100 ìg/ml and 100 µ/ml respectively) (Sigma Co., Madrid, Spain), confirming the absence of Mycoplasma.spp by direct fluorescence with the specific colour agent for ADN (H33233) (Hoescht, Germany). Non-essential amino acids were added when culturing SK-MEL-1. In the case of Melan-a, 2 µM TPA (Sigma), a potent tumour promoter was added to the medium on the day of use. All the processes were carried out in a Cultair ABS type II vertical laminar flow chamber. The melanoma cell lines and Melan-a cultures were kept at 37°C, 98% relative humidity with 5% and 7-10% CO_2 atmosphere respectively in a Cytoperm heater.