الجمهورية الجزائرية الديمقراطية الشعبية

People's Democratic Republic of Algeria

وزارة التعليم العالي والبحث العلمي

Ministry of Higher Education and Scientific Research

جامعة الإخوة منتوري قسنطينة 1

Frères Mentouri Constantine 1 University

Université Frères Mentouri Constantine 1

Faculty of Natural and Life Sciences — **كلية علوم الطبيعة والحياة**

Department of Biochemistry, Molecular and Cellular Biology — **قسم الكيمياء الحيوية والبيولوجيا الخلوية والجزيئية**

Thesis submitted for the award of the Master's degree

Domain: Natural and Life Sciences
Sector: Biochemistry, Molecular and Cellular Biology
Speciality: Biochemistry

Order N° :
Serial N° :

Titled:

A gummy formulation and quality control of Natural diatery supplements for the improvement of digestive disorders, general health and well being.

Presented by: ABDELMOUMENE SALMA
BOUDOURI SIRINE

on: 30/06/2022

Examination board :

Supervisor : Mme MOUAS T NERDJAS (Prof - Mentouri Brothers University, Constantine 1).
Examiner 1 : Pr.DJEDOUANI AMEL (ENS Constantine3)
Examiner 2 : Dr.TABBI AOUATEF (ENS Constantine3)

2021 - 2022

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Dedication

First of all I thank the God who gave me the courage and the patience To achieve my goals. I dedicate this modest work:

To the one who awaits my return at each sunset who has filled me with affection, love and tenderness, and who has watched over my cradle to appease my cries of pain, and who has never ceased to do it forever: My mother (Nora).

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To all my friends, and my relatives without exception whether they are near or far. To all my teachers from primary to higher education.

Sirine

Dedication

First of all I thank the God who gave me the courage and the patience To achieve my goals. I dedicate this modest work:

To my dear parents (MOSTAFA, NORA), for all their sacrifices, love, tenderness, support and prayers throughout my studies,

To my dear brothers (RAHIM, LOQMAN, TAKI) and my beautiful sister (NONA) for their constant encouragement and moral support,

To my dear ADLEN GHERBI You have always offered support and comfort, I express to you a deep admiration, gratitude and unconditional attachment,

To all my friends, and my relatives without exception whether they are near or far. To all my teachers from primary to higher education.

SALMA

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AkT	Ak strain transforming.
ALT	Alanine transaminase.
AST	Aspartate aminotransferase.
BCL-2	B-cell lymphoma 2.
BCL-XL	B-cell lymphoma-extra-large
BV2:	Overflow file below insert point in Doc 2.
CFLIP :	Cellular FLICE-like inhibitory protein.
CIAP1:	Cellular inhibitor of apoptosis protein-1.
COX-2:	Cyclooxygenase-2.
DR4:	Death Receptor 4.
DR5:	Death Receptor 5.
ERK:	The extracellular signal-related kinases.
H9C2:	Cell model used as an alternative for cardiomyocytes.
HEPG2:	Liver Hepatocellular Carcinoma.

HO-1:	Heme Oxygenase Isozyme-1.
HPLC:	High Performance Liquid Chromatography.
IKB:	International Klein Blue.
Il-18:	Interleukin-18.
IL-1β:	Interleukin 1 beta.
Il-6:	Interleukin 6.
Il-8:	Interleukin 8.
JAK/STAT:	Janus kinase-signal transducer and activator of transcription.
JNK:	The c-Jun N-terminal kinases.
LPS:	Local Pet Store.
MAPK:	Mitogen-activated protein kinase.
ML:	Milliliter.
mtDNA:	Mitochondrial DNA.
Nrf2:	Nuclear factor erythroid 2-related factor 2.
OFI:	Optinia ficus indica.

PI3K:	Phosphoinositide 3-kinases**.**
PUFA:	Polyunsaturated fatty acids.
RS:	Rupees.
SOD:	Surface of the ground.
SPME:	Solid-phase microextraction.
TEM:	Transmission Electron Microscopy.
TNF:	Tumor necrosis factor.
TRX:	Total Body Resistance Exercise.
VLDL:	Very-low-density lipoprotein.
XIAP:	X-linked inhibitor of apoptosis.

General introduction

Introduction:

Balanced meals have become a criterion in food selection since the 1980s. Physicians' health and nutritional suggestions, which are increasingly transmitted by the media, impact behavior. With the advancement of modern living, the use of dietary supplements for well-being has expanded significantly: hormonal imbalance, stress, and weariness are at the root of the market well-being. As a result, the market for food supplements has exploded, and it is now the focus of major industrial and commercial concerns.**(Julie VALETTE.,2015).**

Diatery suplements, are food or part of food Playing a significant role in modifying and maintaining normal physiological function that maintains healthy human Beings. The food products used as nutraceuticals can be categorized as dietary fiber, prebiotics, probiotics, polyunsaturated Fatty acids, antioxidants and other different types of herbal natural foods **(Wilfried et Al., 2002).**

Terpenoids, alkaloids, and phenolic compounds are examples of secondary metabolism products produced by plants that are not part of their essential metabolism. Polyphenols are one of the most important classes because they have low toxicity and a wide range of biological benefits, including medical, pharmacological, and dietary applications **(Gurib-Fakim A, 2006).**

The growing interest in preventative medicine stimulates the use of nutraceuticals such as OFI and Curcuma, which provide vital nutritional benefits and can be used as a source of dietary fibres and natural pigments.

The process of extracting and purifying essential oils is extremely basic and straightforward. In vitro or in a still, water vapor flows through plant material. However, these procedures and processes allow for a wide range of variations, which can have a considerable impact on essential oil yield and quality (chemical composition and biological qualities).Furthermore, some research institutions and companies have created new extraction processes for phytochemicals and secondary metabolites that are both safe and environmentally benign. These procedures have a number of advantages, including quicker extraction times and higher-quality oils**. (BOUKHATEM et al., 2019).**

BIBLIOGRAPHIC PART

Chapter I:

Dietary Supplements

I. Dietary supplements:

Ⅰ.1 History:

In France, the first legal definition was established in a multi-sectoral decree in October 1995, which was later adopted by decree no. 96-307 on April 10, 1996. It claims that: : « Food supplements are products intended to be ingested in addition to the current diet, in order to compensate for the actual or supposed inadequacy of daily intakes (…) excluding foods intended for a particular diet and medicines » **(Décret n°96-307 du 10 Avril 1996)**.The European Community defined this notion in 2002 **(Pr Luc Cynober.,2008)**.

The market for food supplements has been growing for some years, particularly in France. Food supplement sales increased by 50% between 2004 and 2007, reaching a record high of one billion euros in 2013 **(MALEYSSON, 2008)**.

Since 2016, when the Algerian functional food market opened to the world in the field of nutrition and nutritional health, a more healthy and scientific consumption of functional food items has grown among Algerian consumers, with the goal of reducing nutrition-related ailments (cancers, diabetes, gastrointestinal system, etc.). Similarly, the concept of food has evolved not only to satisfy hunger, but also for quality, quality and basic ingredients, as well as the percentages of additives in products such as preservatives that cause a variety of diseases, and awareness that these functional food products are capable of maintaining or restoring a healthier state that is increasingly assimilated, for both physical and mental health reasons, and this is what these functional food products offer.**(OUCHERIF, 2021).**

2.Ⅰ Definition:

CAs are defined under **Decree No. 2006-352 2006 and the European Directive** as : « The purpose is to supplement the normal diet and constitute a concentrated source of Nutrients or other substances having a nutritional or physiological effect alone or in combination; marketed in the form of doses, forms of presentation such as capsules, lozenges, tablets, pills and similar forms, as well as powder pouches, liquid ampoules, bottles withdrops and other similar forms of liquid or powdered preparations intended to be taken in measured units of small quantities» **(Décret n°2006-352 du 20 mars 2006).**

Ⅰ.3 Industry:

Food supplements are now commonly promoted without prior scientific review or regulatory registration, in accordance with the code of consumption (which governs food): it is Above all, it is the industry's responsibility to ensure that its products comply with general regulations (safety, labelling, etc.) **(Afssaps, 1997).**

Ⅰ.4 Galenic forms:

Choosing the shape for your product is a strategic form that should not be overlooked. Some types will be more appropriate than others in terms of asset concentration, preservation, protection or preference for use.

Ⅰ.4.1 Solid forms:

Ⅰ.4.1.1 Tablets:

Shapes made up of one or more active substances and excipients that have a variety of appearances, but are usually spherical, solid, and compact (Talbert et al., 2009).They're usually made by compressing a certain volume of particles. The tablets can be taken orally or vaginally. Some are swallowed, while others must be dissolved or disaggregated in water before being administered. Finally, some must remain in the mouth to release the active ingredient **(International Pharmacopoeia,1980; kouonang ,2005).**

4.1.2. Ⅰ Capsules:

Capsules are solid preparations that contain a unit dose of AP and have a hard or soft shell (made of gelatin) of varying form and capacity. The capsules' contents can be solid, liquid, or pasty. The capsules (gel) have a rigid outer shell. Soft-shelled capsules are usually produced, filled, and sealed all at the same time **(Pharmacopoeia European, 2011; Vidal, 2011)**.

4.1.3. Ⅰ Powders:

They are preparations made up of free, dry, and more or less fine solid particles, either in bulk or in single-dose pouches, created by homogeneous mixing of active substances with previously sprayed dry excipients. They could be bubbly **(Champe et al., 2000; Talbert et al., 2009)**.

4.2. Ⅰ Liquid forms:

Oral liquid preparations are usually solutions, emulsions, or suspensions containing one or more active compounds in a suitable vehicle; however, some liquids for oral administration may contain active chemicals that are used as such **(Pebret, 2005).**

4.2.1. Ⅰ Ampoules:

The medicinal product is chemically and microbiologically kept in this pharmaceutical form. B:It is a hermetically sealed closet that can be filled with inert gas to prevent ygene action and sterilized when the active principle permits. The discoloration of the glass acts as a barrier against the light**. (Christen Loock I.,2018).**

Ⅰ.4.2.2 Syrups and bottles:

Syrups are commonly utilized , particularly by youngsters **(Ansel et Al., 1990;Hir et Al .,2001)** Because of its diabetogenic and cariogenic risk **(Hir.,2001)** sucrose, the sweetener most commonly used in various oral fluid forms **(Allen.,2011;Hir et Al .,2001)** and syrups **(Ansel et Al.,1990)** should be avoided as an excipient in drugs intended for diabetics, newborns (A.Hir et Al .,2001), and children. Other sugars **(Lippincott et Al., 2006)** can be used to substitute sucrose **(Allen.,2011; Ansel et Al.,1990; Lippincott et Al., 2006).**

Ⅰ.4.3 Gummies:

Phytochemicals derived from herbs and fruits, according to various studies are a possible alternative to synthetic active ingredients for improving food quality, reducing toxicity, and ensuring environmental safety due to nontoxic biodegradation **(Zhu et al.,1995 ; Choochote et Al.,2005)**.

A gummy bear's basis is typically made up of the jellifying agent (pectins, modified starch, gelatin, etc.) and sugars, with water-soluble elements dissolved and insoluble ingredients suspended in the viscous matrix **(Mueller et al.,2006;Pizzoni et al.,2015).**

As a result, gummies have a wide range of applications in the pharmaceutical and culinary industries as a unique drug delivery mechanism that appeals to children and some adults because to their confectionery appearance and taste. According to several research, the composition of gummy bears, particularly the concentration and origin of the gelling agent and sugars, has a considerable impact on the product's rheological qualities **(Pizzoni et**

al.,2015;Kalviainen et al.,2000).It is considered the most cost-effective and secure form of drug administration **(Thakur et al.,2012).**

Table 01: Some galenic froms from the market.

 Vitamin C 500 dietary supplement	 SOLAR Jar of 60 capsules.
 Cooper Salicylic Acid Powder 1g – 1 bag	 Tonic'Potion 10 ampoules of 10ml Propolia.
 Organic Smokers Syrup 250ml – Herbalgem.	 Santarome Immunit' Bio.

Ⅰ.5 Classification of naturals dietary foods suppliments :

The food sources used as dietary supplements are all natural and can be categorized as:

1. Dietary Fiber
2. Probiotics
3. Prebiotics
4. Polyunsaturated fatty acids
5. Antioxidant vitamin
6. Polyphenols
7. Spices **(kalia .,2005).**

Ⅰ.5.1 Dietary Fiber:

Dietary fiber (DF) is made up of indigestible carbohydrates and lignins found in plants. Functional fiber (FF) is a type of nondigestible carbohydrate that has health benefits for humans (Garima et al., 2016). It's the same one that's in yogurt and other fermented foods. Different strains can aid in the treatment of diarrhea and may also aid in the treatment of other ailments. Lactose, the sugar in milk , cannot be digested by persons who are lactose intolerant **(Garima et al., 2016).**

Ⅰ.5.2 Probiotics :

Lactobacillus It' s possible that this is the most widely used probiotic. It' s the same one that's in yogurt and other fermented foods **(Garima et al., 2016)**.

Ⅰ.5.3 Prebiotics :

Are short-chain polysaccharides with distinctive chemical structures that humans cannot digest; in particular, fructose-based oligosaccharides found naturally in food or added to it. Prebiotic intake boosts the growth of Lactobacillus and Bifidobacteria in the gut, which aids metabolism **(Hord Ng ,2008; Gibson et al.,1999)**.

Fructo-oligosaccharides are abundant in vegetables such as chicory roots, bananas, tomatoes, and alliums.Raffinose and stachyose, both found in beans and peas, are examples of these oligosaccharides. Improved lactose tolerance, anticancer capabilities, toxin neutralization, stimulation of the gut immune system, reduction of constipation, blood lipids,

and blood cholesterol levels are some of the health benefits of prebiotics **(Fuller ,1992; Isolauri et al., 1991; Lin et al., 1989; Sanders ,1994)**.

Ⅰ.5.4 Polyunsaturated fatty acids :

The polyunsaturated fatty acids (PUFAs) are split into two groups: omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFA), with the first double C-bound position varying. Needed fatty acids are two PUFAs that cannot be produced in the human body yet are essential for physiological integrity **(Garima et Al ., 2016).**

Ⅰ.5.5 Antioxidant vitamin:

Antioxidant vitamins include vitamins such as vitamin C, vitamin E, and carotenoids. These vitamins work individually and in combination to prevent oxidative processes that contribute to cancer, cardiovascular disease, cataracts, and other degenerative disorders **(Elliot.,1999).**

Ⅰ.5.6 Polyphenols:

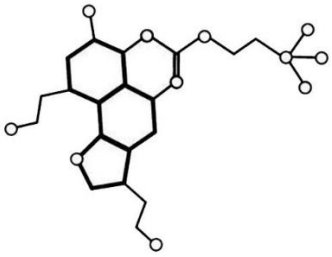
Polyphenols are plant-based phytochemical substances found in fruits, vegetables, whole grains, cereal, legumes, tea, and coffee. Over 8000 polyphenolic chemicals are found in wine and chocolate. phenolic acids, flavonoids, and other compounds **(Ndiaye et al,2008)**, Whole plant diets have been found to contain tilbenes, lignans, and polymeric lignans. These substances are secondary metabolites produced by plants that serve as defensive mechanisms. UV rays, oxidants, and infections are all threats. **(Wang et al.,2010)** Phenolic acids make up about a third of all polyphenolic chemicals in the diet and are divided into two categories:

a) hydroxybenzoic acid derivatives (protocatechuic acid, etc.) and phenolic acids.

B) hydroxycinnamic acid derivatives caffeic acid, kahweol, kahweol, kahweol, kahweo Sinapic acid, coumaric acid, Ferulic acid, chlorogenic acid berries, kiwifruit, cherry, apple, pear, chicory, and Coffee is one of the foods that contains a lot of these phenolic compounds. acidic substances Flavonoids are divided into six categories:anthocyanins, flavonols, flavanols, flavanones, and flavones are all types of flavonoids. and isoflavones; anthocyanins (cyanidin, pelargonidin, etc.); anthocyanins (cyanidin, pelargonidin, etc.); anthocyanins (Red berries (delphinidin, malvidin) are found in the berry family. strawberry, red cabbage, cherry, black grape, and wine **(Ndiaye et al., 2004; Wang et al., 2010).**

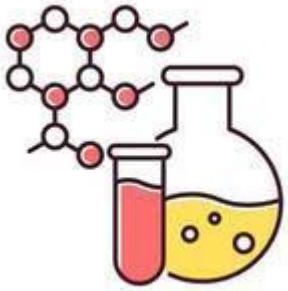
Ⅰ.5.7 Spices :

Since antiquity, spices have been virtually indispensable in the culinary art of flavoring foods. Spices are aromatic vegetable substances that serve as seasoning rather than nutrition in food. They can be whole, broken, or ground. Spice components give meals their distinct flavor, fragrance, and pungency. The pungency comes from volatile oil spices that are responsible for scent, flavor, and oleoresin. Spices are frequently utilized in indigenous remedies, pharmaceuticals, Nutraceuticals, aroma therapy, preservatives, drinks, natural colors, fragrances, dental preparations, and cosmetics, in addition to flavoring and seasoning **(Garima et al., 2016)**.



chapter II:

Natural products and Secondary metabolites



Ⅱ.1 Natural sources of food supplements:

Plants can produce a wide range of products that are not part of their fundamental metabolism, but rather are secondary metabolism products, such as terpenoids, alkaloids, and phenolic chemicals. The latter, also known as polyphenols, are one of the most important classes because they have low toxicity and a wide range of biological benefits, including medicinal, pharmacological, and food applications. They can be found in all parts of the plant (roots, stems, leaves, flowers, pollens, fruits, seeds, and wood) and are engaged in a variety of physiological activities including cell development, seed germination, and fruit ripening. Anthocyanins, flavonoids, and tannins are the most abundant **(Gurib-Fakim A, 2006).**

The most widely used plants on the food supplement market: ginseng, guarana, ginger, valerian, verbena **(Caro et al,. 2010).**

Ⅱ.2 The nutrients:

• Vitamins, minerals.

• Plants and plant preparations

Substances for nutritional or physiological purposes.

• Other ingredients that are traditionally used in food.

• Additives, flavourings and processing aids authorized for use in food and under the conditions prescribed by regulation **(Regulation, 1997).**

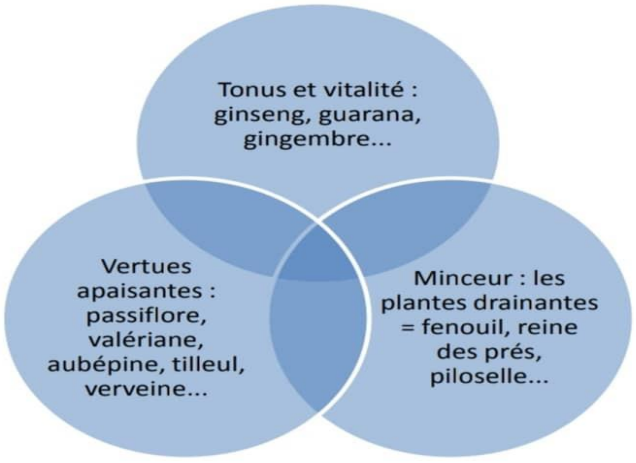


Figure 01: Plant used plants as food supplements **(Caro et al,. 2010)**

Ⅱ.3 Natural product used in the food supplement industry:

The following nutrients are approved in the formulation of food supplements, according to **(VASSON et al. 2007).**

Table 02: Nutritional compounds that have been approved for use as dietary supplements:

Nutritional compounds that have been approved for use as dietary supplements
essential Fatty acids
Antioxidants
Polyphenols
Amino acids
Vitamin A,D,E,K,B1,B2,niacin,pantothenic acid,B6,acid efolic,B12,biotin,c
Minerals calcium,magnesium,iron,copper,iodine,zinc,manganese,sodium,potassium, Selenium,chromium,molybdenum,fluoride,choloride,phosphorus,ect
Plant , plant extracts

Ⅱ.4 Secondary metabolites:

Ⅱ. 4.1_ Definition:

Plants secondary metabolites are naturally generated substances not engaged in plant metabolism. Many secondary metabolites are used in human medicine because they have medicinal qualities **(Hostettmann et Marstonn., 1995).** Secondary metabolites are synthesized in various parts of the cell and stored in vacuoles in particular. They're usually made in one portion of the facility and kept in another. Furthermore, their concentration in the plant frequently varies dramatically over the course of a 24-hour period **(Ravenet et al., 2003).**

.4.2_ Importance of secondary metabolites:

Plant development is helped by secondary metabolites. This is a class of compounds that includes alkaloids, essential oils, and flavonoids. These compounds appear to have an important role in nature **(Hopkins, 2003).**

Organic chemistry specialists and individuals interested in natural substances have researched secondary metabolites for millennia because of their commercial or medical worth. Many secondary metabolism have been proven to play an essential ecological function over the last three decades **(Harborne 1988, Rosenthal et Berenbaum, 1991 ;Paré et Tumlinson, 1997).**

.4.3_Different types of secondary metabolites:

There are three main classes of secondary metabolites in plants: phenolic substances, terpenes and alkaloids **(Ravenet et al.,2003).**

1. phenolics:

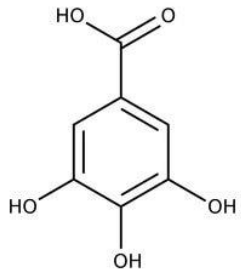
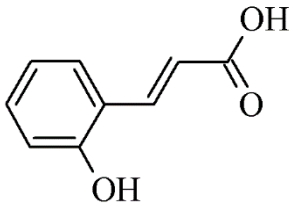
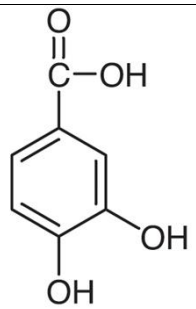
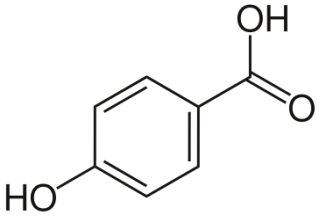
- Phenolic acid
- Tannins
- The coumarines
- Flavonoids
- Anthocyanins

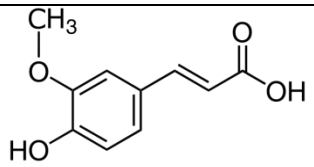
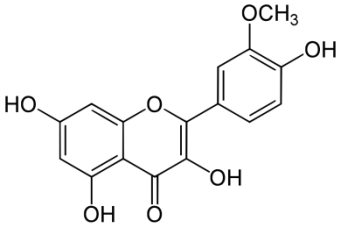
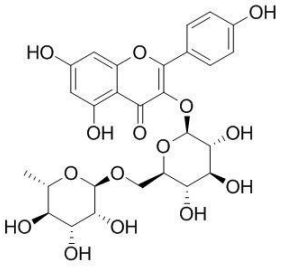
2. Alkaloids :

3. Essential oils:

- Monoterpenes.
- Sesquiterpens.

Table 03: Phenolic compounds of Opuntia ficus indica **(Abidi et al., 2009)**

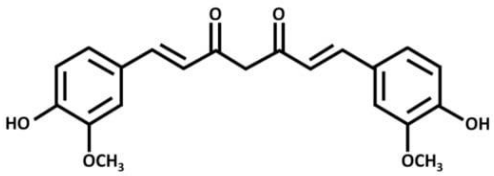
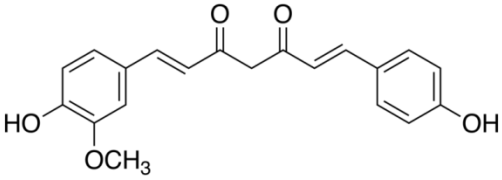
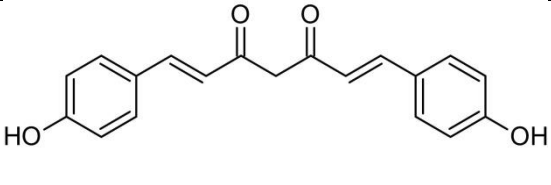
Polyphenols	**Dry matter (mg/100g)**	**Structure**
Gallic acid	0,64-2,37	
Coumaric acid	14,08-16,18	
3,4-dihydroxybenzoic	0,06-5,02	
4-hydroxybenzoic	0,5-4,72	

Ferulic acid	2,29-39,67	
Isorhamnetin-3-O-glucoside	4,59-32,21	
Nicotiflorin	2,89-146,5	

.4.4_The major secondary metabolites of curcuma :

The curcuminoid family consists of three phenolic compounds:

Table 04: Turmeric chemical structures. **(Park et al., 2005).**

Curcumin	
Demethoxycurcumin	
Bisdemethoxycurcumin	

Curcuminoid" is a collective term used for a cluster of compounds such as curcumin, demethoxycurcumin, bis-demethoxycurcumin and cyclic curcumin.**(yoon el al.,2020)**

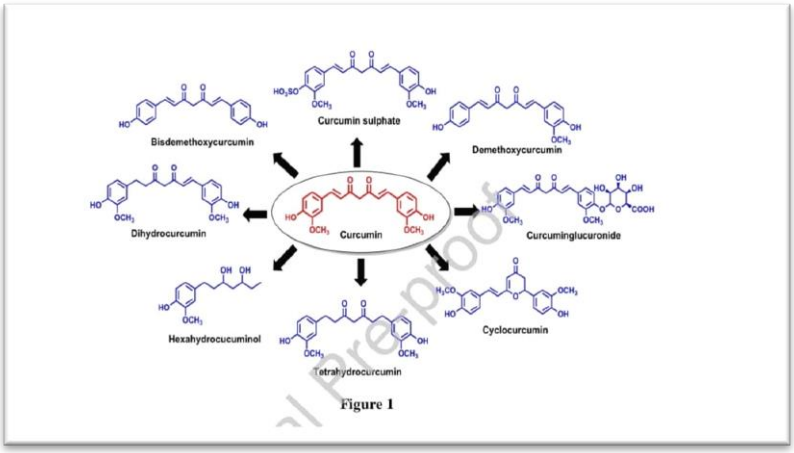
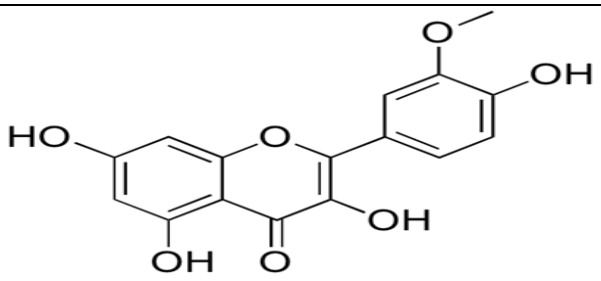


Figure 02: Schematic representation of chemical structures of major curcuminoids isolated from Curcurma longa (turmeric). **(Sethi et al., 2021).**

Commercially available curcumin is not pure curcumin, but rather a mixture of curcumin (approximately 77%), demethoxycurcumin (approximately 18%) and bisdemethoxycurcumin (approximately 5%). **(Anand et al., 2008)**

.4.5_The major secondary metabolites of Opuntia ficus indica:

Identified isorhamnetin glycosides, The major secondary metabolites of Opuntia ficus indica.

Isorhamnetin	

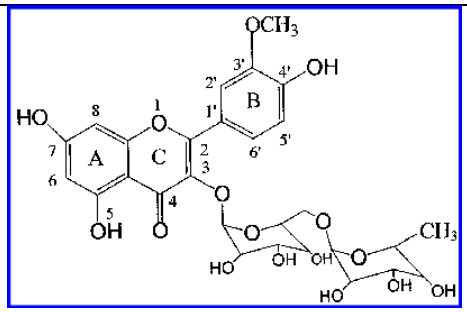
isorhamnetin-3-O-â-rutinoside	

Figure 03: Chemical structure of isorhamnetin **(Gong et al.,2020) and** isorhamnetin-3-O-â-rutinoside **(Galati et al .,2003).**

chapter III:

Opuntia ficus-indica and curcuma generality

Ⅲ.1 Opuntia ficus-indica and curcuma generalities:

Ⅲ.1.1 geographic distribution:

The Algerian cactus culture is generally represented in the agricultural landscape, with the exception of the mountains and Saharan areas, where it is planted on a more regular basis, around communities, in hedges limiting farming or orchard plots **(Arba et al., 2000).** Boumerdès, Blida, Tipaza, Tissemsilt, Chlef, Relizane, Mostaganem, Ain-Témouchent, Oran, Mascara, Sidi-bel Abbès, and Tlemcen are among the wilayas where it can be found **(Benattia, 2017).**

Ⅲ.1.2 Uses of Prickly Fig Parts:

The prickly fig is an excellent example of a species that thrives in dry and semi-arid environments. Its culture is not investment-demanding, yet the revenue it can create is of critical economic value **(Benattia, 2017).**

Furthermore, the nopal is one of the most widely used plants in several economic domains, both as a crop and in its natural condition, and from its roots to its thorns (figs. 4 and 5). **(Benattia, 2017).**

The dietary fibres occurring in OFI can influence polyphenols' bioaccessibility ; in the simulated gastrointestinal conditions, the non-covalent bonds between polyphenols and dietary fibres were probably broken, with consequent polyphenol release in the upper and lower parts of digestive tract, increasing their availability for colonic microbiota action **(Missaoui et al., 2020).**

Figure 04: Packaging of prickly figs and nopals for human consumption in USA **(Inglese, 2018).**

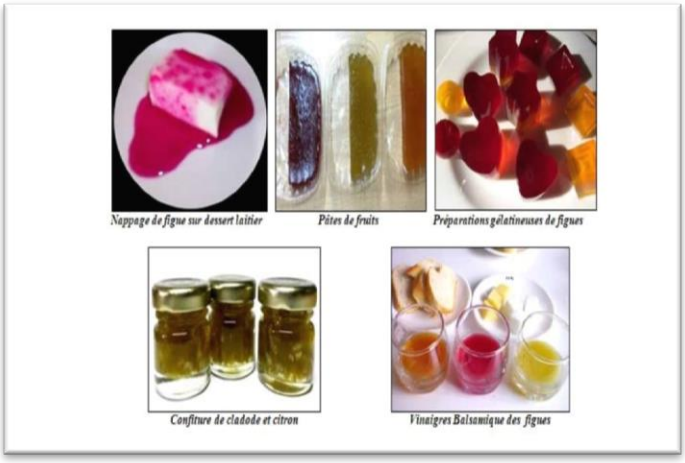


Figure 05: Images of selected prickly fig products in USA **(Inglese, 2018).**

Ⅲ.1.2.1 Human food:

The prickly fig can be eaten raw, cooked, dried, frozen, fermented, or transformed into goods with good sensory quality and microbiological stability, such as juice, nectar, canned, honey, marmalade, alcoholic beverages **(Colanche, Tequila), and jam.... Saenz, 2000; Espirad, 2002; Habibi, 2004; Arba, 2009; Boutakiout, 2015)**

Ⅲ.1.2.2 Animal feed:

The cultivation of Opuntia also generates a lot of interest in the production of fodder, which is its second major purpose, especially in dry and semi-arid regions where it is the only accessible feed stock for cattle at certain periods of the year **(Habibi 2004; Mulas and Mulas 2004).**

Ⅲ.1.2.3 Therapeutic use:

The dietary fibres occurring in OFI can influence polyphenols' bioaccessibility ; in the simulated gastrointestinal conditions, the non-covalent bonds between polyphenols and dietary fibres were probably broken, with consequent polyphenol release in the upper and lower parts of digestive tract, increasing their availability for colonic microbiota action **(Missaoui et al., 2020),** it concequently acts in the intestinal and digestive tract confort.

Its hypoglycemic, lipophilic, antioxidant, and satiogenic qualities are mostly utilized in diet and the treatment of obesity, diabetes, and arteriosclerosis. Treatment for aches and abnormalities of the stomach and intestines. Prevents ulcers in the stomach.

It is used to prevent stomach ulcers and gastrointestinal diseases due to its anti-ulcerative, anti-inflammatory, and antispasmodic qualities. Some studies have demonstrated that it can help with the treatment of alcoholism's repercussions. Fruits can also help with diarrhoea. Its diuretic and antioxidant properties are increasingly being considered.

Modern research has not only validated the benefits of the nopal, which were previously exclusively acknowledged by traditional medicine, but it has also discovered new qualities each year. Abscesses, horns, calluses, boils, and all intestinal and cutaneous inflammations were historically treated with opuntia **(Schweizer 1999).**

Dried flowers are often used to prepare diuretic herbal drinks, which help to ease kidney pain.

Ⅲ.1.3 Biological Activities:

The chemical profile of prickly pear has revealed that it is an essential source of vitamins, minerals, fiber, certain amino acids, and fatty acids with possible health advantages. Phytosterols, flavonoids, and polyphenols are among the beneficial components present in its compsition.**(Silva et al.,2021)**

Ⅲ.1.3.1 Anti-inflammatory activity :

Many studies have found that employing fruit extract, lyophilized cladodes, or phytosterols from fruit and stem extracts, Opuntia has analgesic and antiinflammatory properties **(Allegra et al,. 2014; Kemi et al,. 2006; Panico et al,.2007; Tesoriere et al. 2014)** Furthermore, B-sitosterol extract from the cactus stem has been shown to have anti-inflammatory properties in Opuntia ficus indica **(Allegra et al. 2014).**

This is the first proof of B-Sitosterol lyophilized aqueous extract of Opuntia ficus indica fruit's anti-inflammatory effect.

Ⅲ.1.3.2 Anti-ulcer activity:

Opuntia ficus indica cladodes are used in Sicilian traditional medicine to heal gastric ulcers and their cicatrisant effect .The effect of lyophilized cladodes on an ethanol-induced ulcer in a rat was studied, and ultrastructural changes were found using TEM, supporting the protective effect of lyophilized cladodes administration. It's possible that mucilage from Opuntia ficus indica was the primary antiulcer component **(Galati et al,. 2003).**

Ⅲ.1.3.3 Antioxidant activity:

The mechanism of antioxidant activity of an ethanol extract of Opuntia ficus indica stem was investigated. In the thiocyanate assay technique, the ethanol extract inhibited linoeic acid oxidation in a concentration-dependent manner. The extract also shown dose-dependent free radical scavenging activity. As a result, the ethanol extract was discovered to have the capacity to protect plasmid DNA from strand breakage caused by hydroxyl radicals. The ethanol extract was shown to have a significant concentration of phenolic chemicals, which are responsible for the extract's antioxidant effect **(Butera et al,. 2002; Gentile et al,. 2004).**

Ⅲ.1.3.4 Anti-diabetic activity:

In Mexico, prickly pear cactus stems have long been used to treat diabetes **(Almimi et al. 2010)**. Opuntia spp. have recently become one of the most popular products advised by Italian herbalists for decreasing glycema **(Morales et al. 2012).**

Some Phyto products based on O. ficus-indica are produced in Algeria so basically they are available on the Algerian market:

Figure 06: O. ficus-indica based in Algerian Market

Ⅲ.2 Curcuma longa:

Turmeric (Curcuma longa) is a ginger family that is abundantly produced in the southern and south western tropical Asia regions. Turmeric, which is used as a spice in Iran, Malaysia, India, China, Polynesia, and Thailand, has an effect on the nature, color, and flavor of dishes. Turmeric has also been used in India and China for ages to cure disorders such dermatologic diseases, infection, stress, and depression. Turmeric's health benefits are mostly attributed to a lipophilic polyphenol compound called "curcumin," which is obtained from the

herb's rhizomes and is orange-yellow in color .Curcumin is known recently to have antioxidant, anti-inflammatory, anticancer effects and, thanks to these effects, to have an important role in prevention and treatment of various illnesses ranging notably from cancer to autoimmune, neurological, cardiovascular diseases, and diabetic. Furthermore, it is aimed to increase the biological activity and physiological effects of the curcumin on the body by synthesizing curcumin analogues **(Kocaadam et al., 2017).**

And since curcumin is the majority compound of Curcuma longa L, we propose in the following to study its therapeutic properties.

Ⅲ.2.1 Biological activities and molecular targets of curcumin and related diseases :

Curcumin first appeared in Ayurvedic medical treatment procedures in India, where it was used to cure injuries, skin illnesses, eye infections, ambustions, and acne **(Hatcher et al., 2008).**

Curcumin has been found to be effective in the treatment of cancer, autoimmune illnesses, metabolic diseases, neurological diseases, CVDs, lung diseases, liver diseases, and a range of other inflammatory diseases in the last 30 years **(Aggarwal and Harikumar, 2009; Kannappan et al., 2011).**

It is believed that regulation of these molecular targets that play a role in the disease's creation process is possible. It has been demonstrated, for example, that tumor formation can be slowed by inhibiting the signaling pathways of cancer cells . **(Devassy et al., 2015).**

Curcumin's polyphenol structure has been proven to efficiently regulate molecular targets involved in the development of a variety of illnesses (Fig. 7).

Curcumin has a feature that boosts free radical scavenging activity due to its structure's proclivity for high-level methoxylation and low-level hydrogenation. Curcumin's anticancer, anti-inflammatory, and antioxidant properties are thought to be due to this structure **(Devassy et al., 2015). (Fig. 7).**

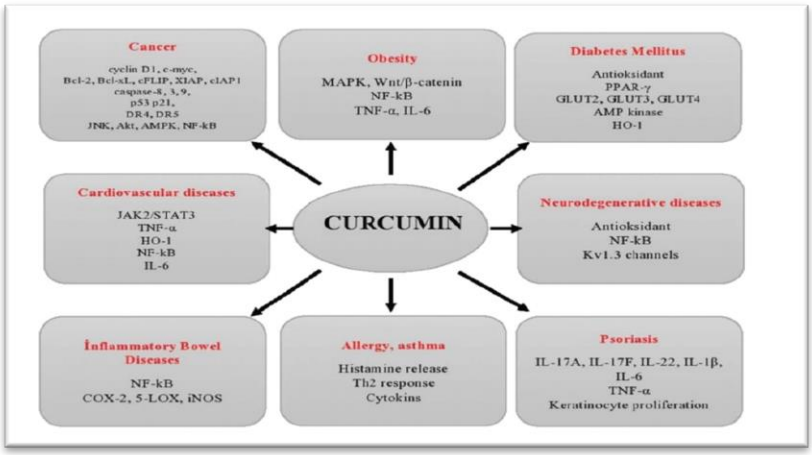


Figure 07: Related molecular targets and diseases of curcumin **(Devassy et al., 2015).**

❖ **Skin anti aging and disorders:**

It was suggested that nanoformulation of curcumin may act as anti-aging and wound-healing formulations. Downregulation of β1-integrin plays the main role in skin aging. Nano-formulated curcumin can increase increased β1-integrin gene expression, and increased Bcl2/Bax ratio, and also NFκB expression in fibroblast cells. **(Tavakol et al.,2019),** so it acts at internal level mainly by dermal cell regeneration in anti aging activity.

Ⅲ.2.2. Anti-cancer properties:

Even curcumin has been shown to have a beneficial effect against a variety of diseases; however, its impact on cancer is the most understudied **(Devassy et al., 2015).**

❖ **Skin disorders:**

Downregulation of β1-integrin plays the main role in skin aging. Nano-formulated curcumin can increase increased β1-integrin gene expression, and increased Bcl2/Bax ratio, and also NFκB expression in fibroblast cells. It was suggested that nanoformulation of curcumin may act as anti-aging and wound-healing formulations **(Tavakol et al.,2019)**

Curcumin has been demonstrated to be beneficial in suppressing transformation, tumor development and invasion, angiogenesis, and metastasis in several stages of cancer development. Curcumin has been shown to inhibit tumor cell growth via the cell proliferation

pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, and cIAP1), caspase activation pathway, tumor suppressor pathway, death receptor pathway (DR4, DR5), and many cell signal pathways that contain protein kinase pathway (cprotein kinase (AMPK)) **(Ravindran et al., 2009).**

Curcumin has been shown to be useful in reducing or preventing a variety of malignancies, including multiple myeloma, colon, pancreas, breast, prostate, and lung cancers **(Anand et al., 2008; Devassy et al., 2015).**

In a study on colon cancer cells, a monocarbonyl analogue of B63 obtained through chemical changes of curcumin's structure was found to have a stronger antiproliferative impact than curcumin. Simultaneously, by using less B63 (50 mg/kg B63, 100 mg/kg curcumin), tumor growth was suppressed, similar to curcumin **(Zheng et al., 2014)**.

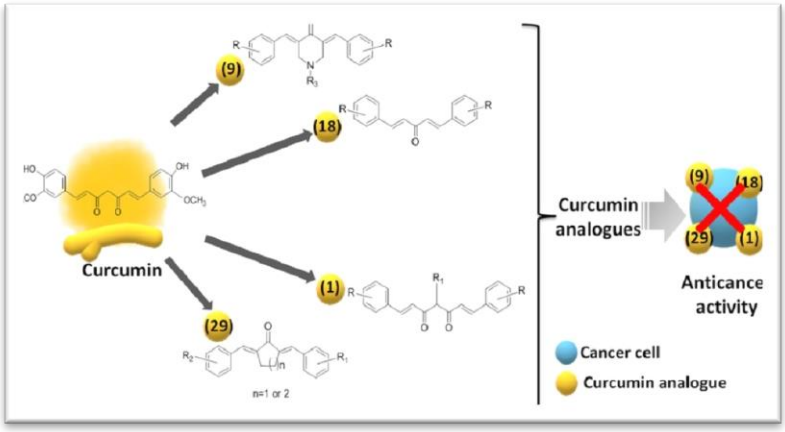


Figure 08: Graphical abstract **(Sethi et al.,2021).**

Ⅲ.2.3Anti-inflammatory and antioxidant effects:

Curcumin has been discovered to have anti-inflammatory and antioxidant properties **(Deogade and Ghate, 2015).**

Curcumin's hydroxyl and methoxygroups are thought to be responsible for these characteristics **(Rahman and Biswas, 2009).**

Curcumin inhibits proinflammatory interleukins (IL-1, 2, 6, 8, and 12), as well as cytokines (tumor necrosis factor-alpha (TNF-a), and monocyte chemoattractant protein-1) via the janus kinase and signal transducer and activator of transcription (JAK/STAT) signaling pathways. Curcumin is also said to modulate the inflammatory response by inhibiting the

activity of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), lipoxygenase, and xanthine oxidase enzymes, and therefore may limit NFkB activation **(Rahman and Biswas, 2009).**

Curcumin is said to work by reducing inflammatory cell proliferation, metastasis, and angiogenesis by interacting with a variety of molecular targets **(Shehzad et al., 2013).**

Inflammation alters signal pathways, which is linked to an increase in inflammatory biomarkers, lipid peroxides, and free radicals, according to large-scale research. Inflammation, both acute and chronic, is a major risk factor for cardiovascular, neurological, and metabolic illnesses, as well as obesity, type 2 diabetes, and some cancers **(Dantzer et al., 2008; Medzhitov, 2008).**

Ⅲ.2.4 Cardiovascular diseases:

Opment of heart and circulatory disorders (CVD). Curcumin is said to have an anti-inflammatory effect against CVD through a variety of ways. Curcumin is said to activate the Nrf2-dependent antioxidant response element, allowing HO-1 expression. Curcumin is also said to decrease TNF-a in vascular and aortic smooth muscle cells, as well as boost p21 expression via the HO-1 pathway. **(Wongcharoen and Phrommintikul, 2009; Pae et al., 2007).**

In a research examining the effects of curcumin on cardiovascular risk factors in people with coronary artery disease, it was discovered that those who took curcumin had significantly lower serum triglyceride, LDL, and VLDL cholesterol levels. Despite the fact that curcumin has been shown to have positive effects on blood lipid profiles, no significant impacts on inflammatory markers have been discovered **(Mirzabeigia et al., 2015).**

Turmeric was discovered to be one of the most popular herbal foods in a study conducted in Turkey on the consumption prevalence of plant-based alternative treatments and supplementary foods among people with CVDs. Additionally, the most common causes for patients to use alternative goods include hypertension and hyperlipidemia **(Ipek et al.,2013).**

Ⅲ.2.5. Neurodegenerative diseases:

Neurodegenerative illnesses are associated with aging, which is a substantial risk factor. Curcumin is thought to be beneficial against aging mechanisms, preventing changes in cell proteins that occur as a result of age. As a result, curcumin appears to assist preserve protein

homeostasis and may be useful in the prevention of aging-related illnesses. **(Monroy and colleagues, 2013).**

Abnormal protein formation produces gene alterations like human amyloid precursor protein or presenile 1 or 2 in neurodegenerative illnesses like Alzheimer's, which are characterized by inflammation and oxidative stress **(Smith et al., 2007).**

Curcumin's antioxidant and anti-inflammatory qualities have been shown to improve cognitive abilities in Alzheimer's patients, and it has also been linked to reduced b-amyloid plaques and microglia production, as well as delayed neuron degradation. **(Mishra and Palanivelu, 2008).**

The loss of dopaminergic neurons in the substantia nigra is a hallmark of Parkinson's disease (PD), one of the most common neurodegenerative disorders. Curcumin's antioxidant action is the most important biological effect associated to neuroprotection **(Mythri and Srinivas Bharath, 2012).**

In the 6-OHDA rat model of Parkinson's disease, it preserves substantia nigra neurons and improves dopamine levels. Curcumin protects numerous tyrosine hydroxylase-positive cells of the substantia nigra, and it is thought to sustain dopamine levels in the stratum as a result of this function **(Zbarsky et al., 2005).**

Curcumin also inhibits channel Kv1.3, which is mostly active in T(EM)cells, while suppressing cytokine release and proliferation in T(EM) cells isolated from Ms patients **(Lian et al., 2013).**

Ⅲ.3 The safe dosage and toxicology of curcumin :

Curcumin don’t present any toxicological effect , **(2019)**

Ⅲ.4 Curcumin Solubility :

Curcumin can be isolated from Turmeric by different ways, it is not hydrosoluble, and more effectively extracted and soluble in Hexane, acetone, dichloromethane, methanol and ethanol. Acetone gave the highest extraction efficiency, in adition to a reactive chemical form due to the ph acidity which confer a keto-enol form totomerisation. The present work evaluated novel surfactant based water-in-DES micro emulsion system as a potential solvent system for solubility and stability of curcumin. Under the optimized conditions, excellent

uptake of curcumin was observed in this system as compared to that in water, ionic liquid, and other DESs.**(Dhingra et al .,2021).**

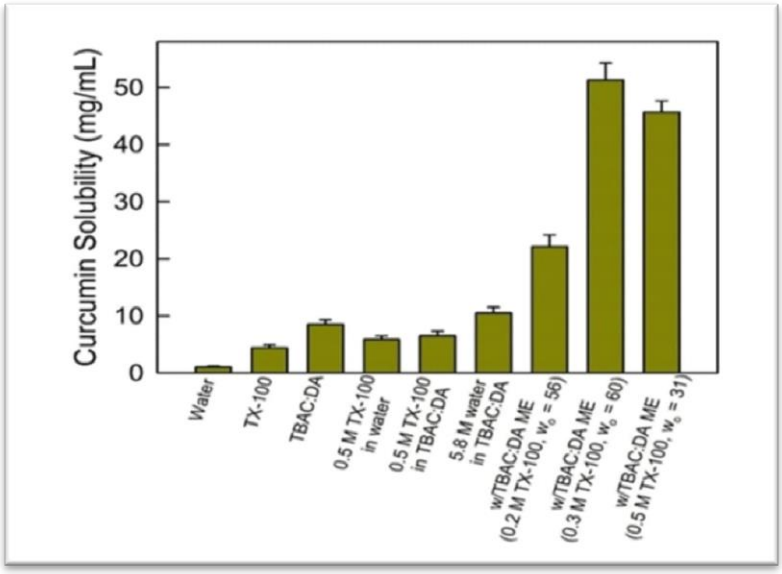


Figure 09: Bar chart depicting curcumin solubility (mg/mL) in different solvent systems. **(Dhingra et al .,2021)**

Table 05: Several food supplements based on turmeric are available in the Algerian market, such as:

Nutribio® Articulation. is a dietary supplement based on Curcuma's patented phytoactive ingredients for:

- An effective and natural solution for joint comfort .
- Increases joint mobility and flexibility.
- Marketed by Biopharm, a pharmaceutical company committed to quality.

(Nutribio.dz)(site web).

COREFOOD Gélules De Concentré De Curcuma - Anti-Inflamatoire Naturel:

- Anti-inflammatory
- Contributes to joint protection
- Improves digestive comfort
- Maintains liver health

(jumia.dz)(site web).

Biomax curcuma :

- Stimulant: turmeric fights against gastric acidity by stimulating mucus secretions.
- Blood thinner: Turmeric helps treat circulatory problems and, as a result, reduces the risk of stroke and heart attack.
- Dermatological problems: eczema, mycosis, psoriasis.

(Biomax .dz)(site web)

□.5. Pharmacovigilance:

□.5.1. Definition of pharmacovigilance:

Pharmacovigilance is the science and practice of detecting, assessing, understanding, and preventing adverse responses to marketed medications and other problems. This involves risk management and the prevention of drug errors, as well as the dissemination of product information, actions to promote the sensible use of medicinal products, and crisis preparedness. I.S.D.B., WHO, 2005) **(source : site web).**

□.5.2. Objective of Pharmacovigilance:

Pharmacovigilance is at the heart of public health. It allows:

- Improve clinical practice;
- Promote the rational use of drugs;
- Propose measures to reduce the risks and severity of the effects adverse reactions related to the use of all products (drugs, vaccines);
- Constantly evaluate the benefits/risks of medicines;
- Improve information on risk and its prevention;
- Ensure patient safety;
- Participate in research and training.

Thus, pharmacovigilance is a shared responsibility among all stakeholders in the health system in an atmosphere of trust, confidentiality, consultation and synergy. **(Source :site web).**

□.5.3. Interest: pharmacovigilance has a dual interest:

1. For the patient:

- Better safety in the use of drugs.
- Better management of adverse reactions.

2. For the community:

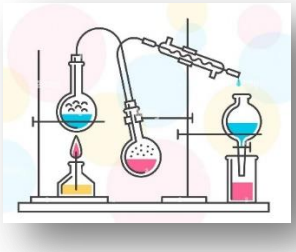
- A decrease in morbidity and mortality related to the occurrence of effects undesirable drugs.
- Past experiences lead to better protection of pharmacovigilance patients**. (Source :site web).**

❖ Pharmacovigilance in Algeria:

The Algerian system of Pharmacovigilance is under the supervision of the Ministry of Health, Population and Hospital Reform www.cnpm.org.dz

Note :

Regulations concerning medical devices, reagents, medicinal plants, cosmetic products, food supplements are not mentioned in this guide. **(** www.cnpm.org.dz**)**



chapter IV:

Bioactive compounds extraction

Ⅳ.1 Extraction methods used in industry:

Ⅳ.1.1 Decoction:

It can be used to extract hard or extremely hard plant materials such as wood, bark, roots, or plants with poorly soluble components. The therapeutic components are extracted by boiling fresh or dried plants in water for 10 to 30 minutes **(Baba-Aïssa,2000 ; Kraft et al,2004).**

Ⅳ.1.2 Infusion:

Infusion is a process of extracting a substance's active components or fragrances by dissolving it in a hot liquid that cools down **(Nguyen, 2010)**. The product is then filtered to obtain an injected version **(Pradal, 2016).**

Ⅳ.1.3 Maceration:

Maceration is a liquid-solid extraction process that takes 30 minutes to 48 hours at room temperature. For several hours or even days, in cold water (aqueous maceration) or vegetable oil (oily maceration), to allow active ingredients to distribute well **(Kraft et al, 2004)**.In the lack of boiling, this approach poses a danger of bacterial contamination of the finished product **(Nguyen,2010)**.

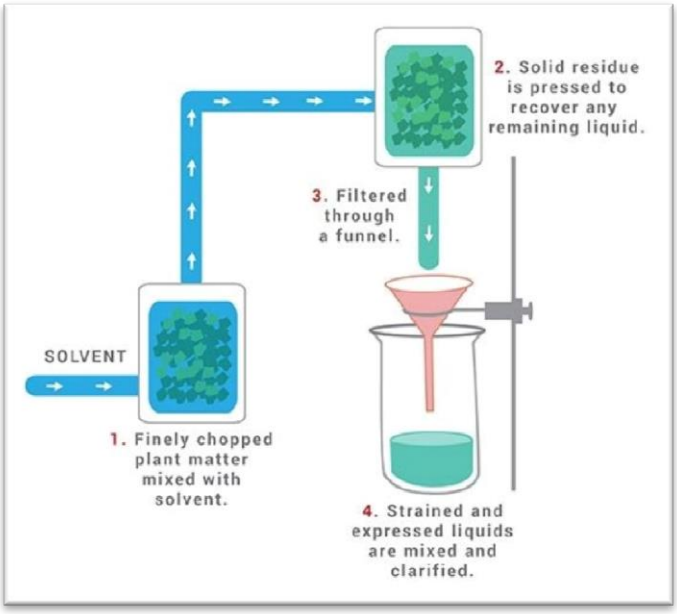


Figure 10 : Schematization of maceration **(Delaroche,2020).**

Ⅳ.1.4 Distillation:

With a voltage steam at 100°C, is suited to substances with low or no water solubility. This ancestral technique, which contains three variants: steam drive, hydrodistillation, and hydrodiffusion **(Desmares et al.,2008).**

Ⅳ.1.4.1 The steam engine :

This method has the advantage of avoiding direct contact with the plant material to be treated with water, whether it is fresh or dried. The method entails infusing water vapour from a boiler at the bottom of a vegetable load that has been placed in a still atop a grid . The oleiferous cells burst and release their essential oil content as water vapour flows through the plant.Water vapour that has been charged with plant compounds is recovered and condensed at the level of a coil that acts as a condenser, where cold water circulates before being channeled to a tree or Florentine vase. The essential oil is then separated into two phases, one aqueous (floral water) and the other hydrophobic (organic). After the cooled distillate settles, the difference in density is used to separate it. Depending on the location of HE secreting cells, this extraction can be quick or gradual **(Saidj,2007)**.

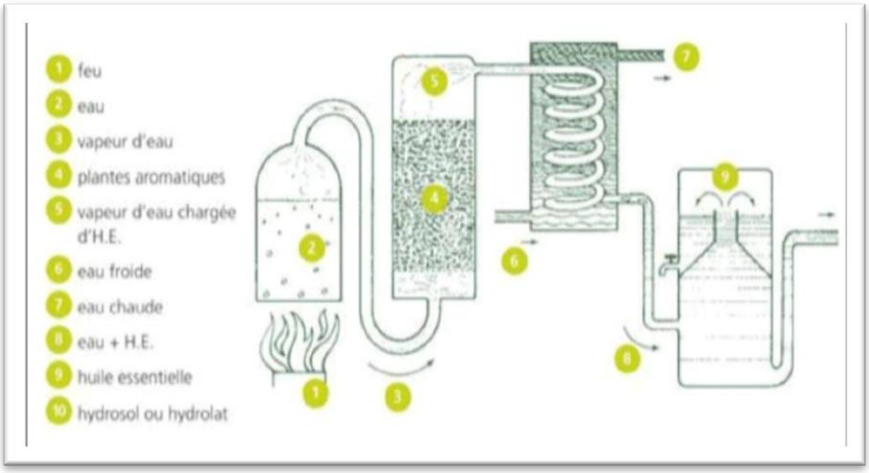


Figure 11: Schematic of Steam Driven Distillation **(Pranarôm, 2016).**

Ⅳ.1.4.2 Hydrodiffusion :

Steam distillation is a type of hydrodiffusion. It works by driving water vapour through plant matter from the top down. The utilization of gravity to push and condense the mixture of water vapour, HE » distributed in plant materials is unique. The vapour flow is descending as

water vapour is injected in the direction of gravity. Furthermore, although this vapour is totally saturated, it is not hot. Essential oil flows into a collector, allowing for air pressure equilibrium **(Li et al., 2014)**.Hydrodiffusion, like steam drive, has the advantage of avoiding contact between plant material and water. Furthermore, hydrodiffusion is faster than water vapour drive, saving energy and allowing for higher essential oil concentrations **(Bruneton,2009).**

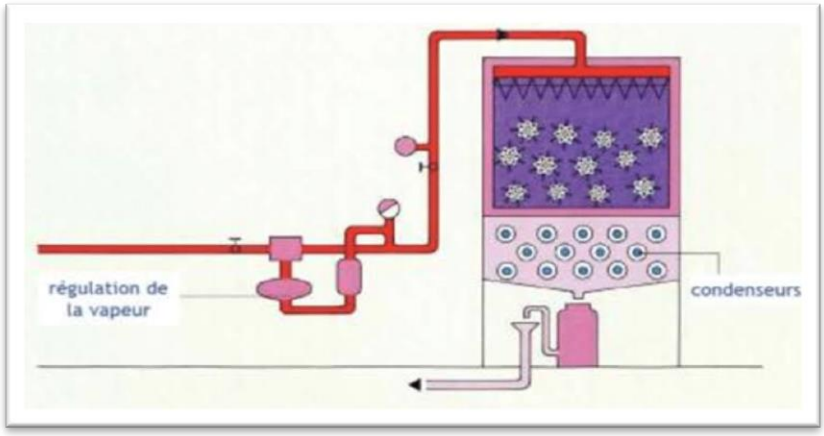


Figure 12: Hydrodiffusion montage **(Pranarôm, 2016).**

Ⅳ.1.4.3 Hydrodistillation :

The raw material is in direct contact with water during hydrodistillation . The plant raw material, which might be cool or dry, is immersed in a water bath during the procedure. The plant can be totally submerged or float at the surface of the water, depending on the density of the foliage and the amount of material each load. The whole is then boiled, usually under pressure, by superheated steam fed into a double envelope intended for that purpose or around the still, or by direct heating to the base of the still by various fuels **(Lucchesi ,2005)**.

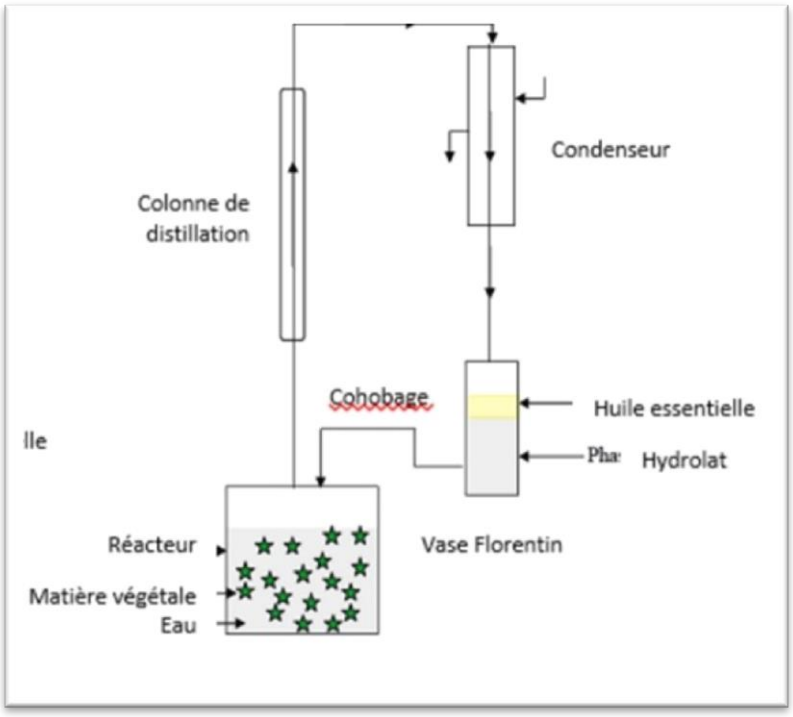


Figure 13: Hydrodistillation montage **(Farhat, A.,2010)**.

Ⅳ.1.5 Swelling of fat or saturated maceration:

Swelling is often reserved for relatively low flower essence concentrations. This approach makes use of the solubility of essential oils in fat, as well as the ability of the latter to absorb odors spontaneously. It can be done hot or cold, depending on the plants' fragility and suitability for heat resistance **(Degryse et al.,2008)**.

Ⅳ.1.5.1 Cold Swelling:

This method, is usually reserved for delicate flowers (such as jasmine, tuberose, daffodil, or carnation) that retain their scent after being picked but cannot be heated (the molecules to be extracted are denatured by distillation).The petals are exposed to refined lipids (typically animal) that are odorless and absorbent, and are dispersed over glass walls supported by wood.

The compounds released by the flowers are cold diffused into the fat, which eventually saturates in essences while preserving the odorous ingredients. The flowers are discarded as they diminish and replaced with fresh flowers on a regular basis until the fat is totally soaked in aroma.We receive a form of fragrant ointment (ointment floral) at the conclusion of the swelling that can be utilized as is for the creation of cosmetic products, or we can treat alcohol

in threshers to discharge it from its fat. It enables the absolute extraction of alcohol after vacuum evaporation **(Desmares et al.,2008)**.

Ⅳ.1.5.2 Hot Swelling:

This extraction process, which has been around since antiquity, was developed in tandem with advancements in other extraction procedures. It's designated for flowers that aren't as delicate as those removed by cold swelling, such as violet, blackcurrant, and orange blossoms **(Bruneton ,1993)**.

The process of infusing flowers into fat, usually pre-heated fat, is known as hot swelling or maceration.After cooling, the resulting mixture is boiled and filtered to remove the impurities.

We also get a floral ointment here to get rid of the exhausted raw material. Separating the lipids and chemical odorants is easier with a cold wash in pure alcohol. There is also an absolute once the alcohol has evaporated. It is no longer widely used **(Bruneton,1993)**.

Ⅳ.1.6. Extraction using volatile solvents:

In this technique, a solvent is used to deplete the plant's volatil, which evaporates leaving a waxy, colorful, and scented residue known as « concrete. » **(Duraffourd et al., 1990 , Belaiche.,1979).**

Selectivity (power solvent for odorous constituents), stability, chemical inertia, boiling temperature not too high to allow total elimination, not too low to avoid losses and thus a rise in costs, and security of non-toxic or flammable handling are all influenced by technical and economic parameters. Aliphatic hydrocarbons such as petroleum ether and hexane, as well as propane and liquid butane, are the most often used solvents (under pressure). Even though benzene is a good solvent, its toxicity is limiting its use. Halogenated (chlorinated and fluorinated derivatives of methane and ethane) and ethanol are also utilized as solvents.The solvent is distilled after extraction, and the plant material is recovered by infusing water vapour into it at the end of the operation **(Bruneton,1993)**.

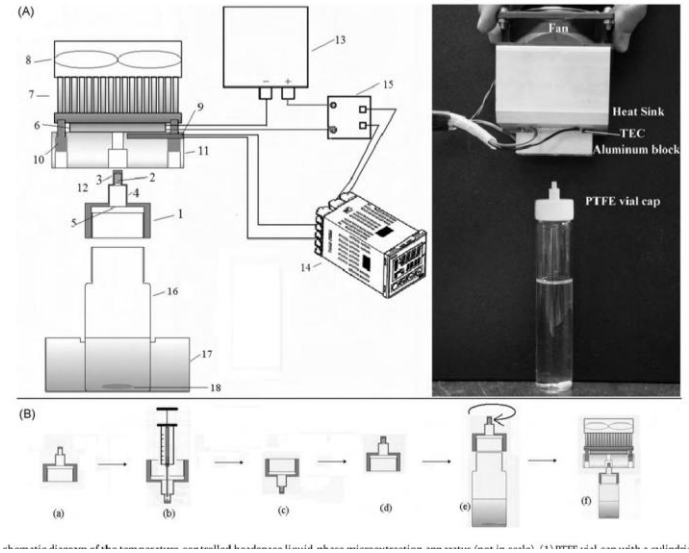


Figure 14: (A) The temperature-controlled headspace liquid-phase microextraction device is depicted schematically (not in scale).

(1) A PTFE vial cap having a cylindrical cavity, (2) an extractant, (3) a cavity, (4) a transit region, and (5) a transit region entry (6) PTFE vial cap screw threads TEC, heatsink, fan, PT-100 temperature sensor, nylon screw, (12) two-step hole in aluminum block, (13) aluminum block, (14) power supply, (15) digital temperature controller, (16) solid state relay, (17) cylindrical vial, (18) magnetic stirrer with water bath, and (19) PTFE stirrer There were no heat insulating materials on display. (B) The TC-HS-LPME technique. (a) Vial cap made of PTFE (a) without extractant, (b) with extractant, (c) with extractant in PTFE vial cap, (d) with extractant suspended constantly in cavity(d) suspending the extractant in the cavity at the top of the cap, $ fastening the cap onto the sample vial, and (f) attaching the cooling system to the PTFE vial cap. (Chen et al.,2010) The genuine picture of the TC-HS-LPME gadget **(Chena et al.,2010).**

Ⅳ.1.6.1 Maceration :

During a solid extraction – liquid by organic solvent, heat is transferred first by conduction from a hot wall, then by convection in the extraction medium (sometimes forced by agitation) **(Li et al., 2014)**.

Ⅳ.1.7. The cold expression :

The petrol, which can be affected by water vapour, is extracted from fresh citrus fruit pericarp using various methods : in industry, the zest is dilaced and the contents of the drying bags are recovered by hand or by machines that split the pockets by expression and collect essential oil directly **(Bruneton ,1993).**

On the one hand, this artisanal method is completely abandoned in favor of machinery used in the extraction of fruit juices, while on the other hand, this artisanal method is completely abandoned in favor of machinery used in the extraction of fruit juices **(Belaiche ,1979)**.

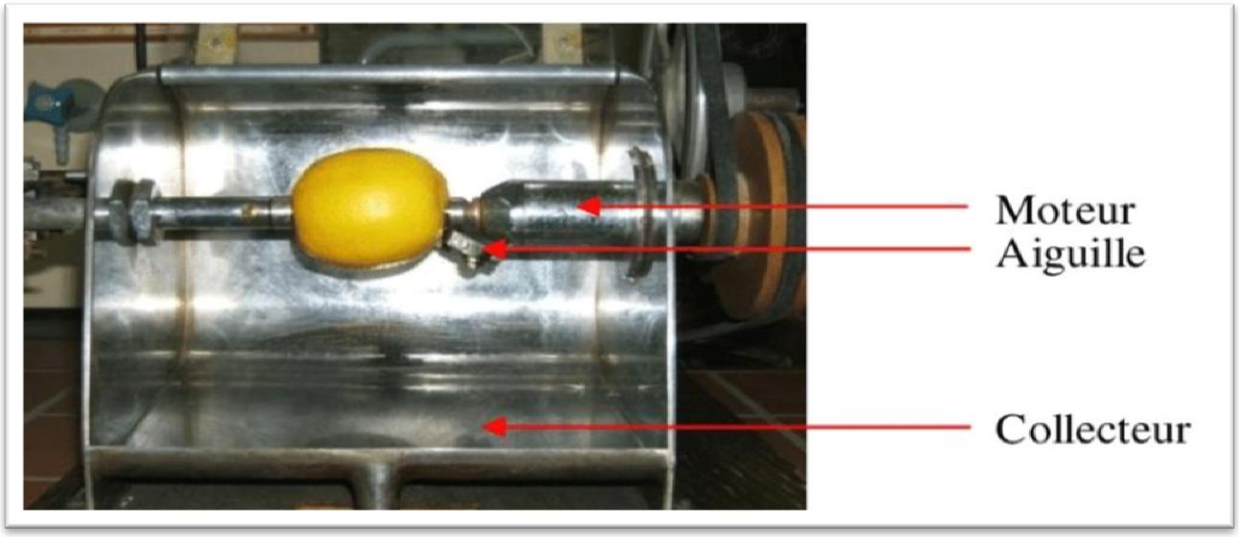


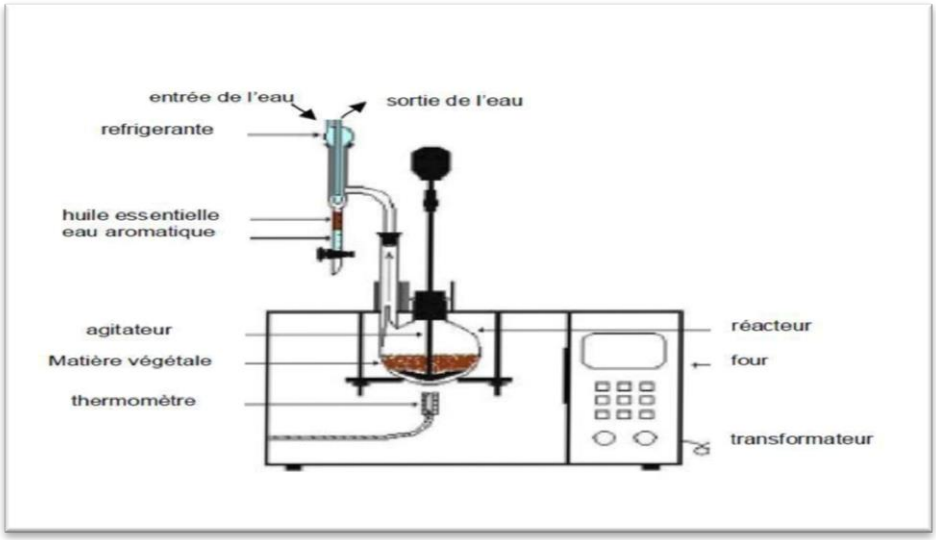
Figure 15: Diagram of the mounting of the "cold expression" **(FARHAT. A., 2010)**.

Ⅳ.1.8 Microwave extraction:

is a method of extracting compounds from material fast and selectively utilizing microwaves and clear solvents **(Paré.,1997)**.

In the microwave, plant material is immersed in a transparent solvent, allowing just the vegetable to be heated. Water in the glandular system plant will be heated by microwaves, generating volatile compounds that will pass through the solvent (not heated). The extract is filtered and then recovered. Microwave extraction provides the significant advantage of lowering extraction time to a few minutes **(France Ida, 1996)**.

This is how it works ,Fast and energy-efficient, it produces a product that is frequently of higher quality than traditional hydrodistillation **(Bruneton,1993)**. Furthermore, according



to **(Scheffer.,1996)**.

Figure 16: Schematic principle of microwave hydrodistillation apparatus **(Lagunez-Rivera, 2006)**.

Ⅳ.1.9 Ultrasound-induced:

microcavitations damage the structure of plant walls, particularly cellulose crystalline zones, resulting in ultrasonic extraction. Ultrasound promotes diffusion and may change the order in which essential oils are distilled. For low boiling point solvents and extraction temperatures below boiling point, ultrasonic extraction is the preferred method. The fundamental benefit of this method is that it reduces extraction time, increases extract yield, and makes it easier to extract thermosensitive compounds **(Lagunez-Rivera ,2006)**.

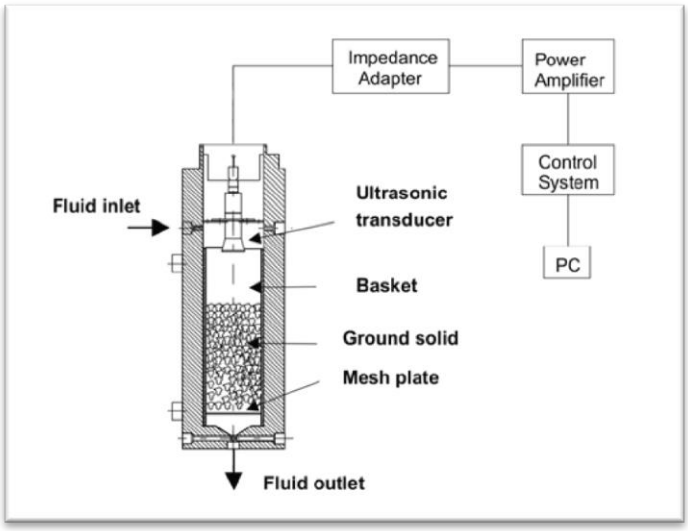


Figure 17: Schematization of Ultrasonic extraction assembly **(Riera et al.,2004).**

Ⅳ.1.10 Supercritical fluid extraction :

In the case of plants deficient in essential oils, a relatively new technique appeared to be useful for increasing production. It extracts the components from the plants using supercritical fluids .Indeed, supercritical fluids acquire features such as high solid diffusibility and solvent power when heated and pressured beyond the critical point .Several gases are now employed in this manner .Carbon CO2 has received special attention because it has unquestionable advantages : it is a natural product that is chemically inert, non-flammable, non-toxic, easy to eradicate totally, selective, widely available, and inexpensive **(Bruneton , 1993 ; Wichtl and Anton,1999)**.

Compressing carbon at pressures and temperatures over its critical point (P =72.8 bars and T= 31.1°C) is known as supercritical fluid extraction. The resulting fluid travels past the product to be treated and the charge in to extract, then relaxes and enters the gas phase before separating from the extracted molecule. CO2 is used to extract essential oils.Supercritical oils, according to **(Scheffer,1996)**.

have a shorter extraction time than conventional procedures.**(Bruneton,1993).**

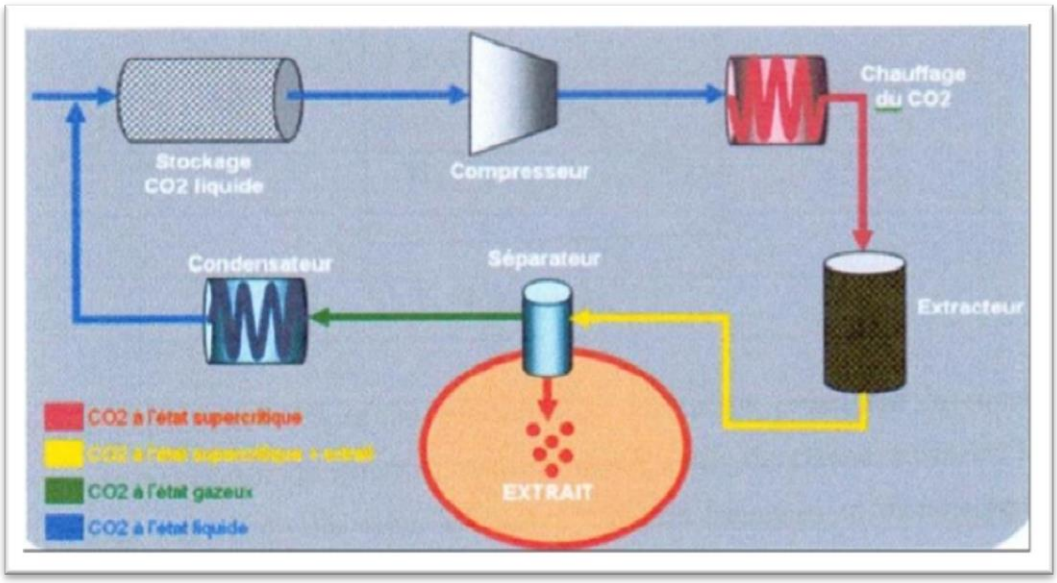


Figure 18: Diagram of the principle of supercritical CO2 extraction technique **(Pourmortazavi, 2007).**

Ⅳ.1.11 Extraction by headspace of –SPME :

Supelco (Bellefonte, PA, USA) first commercialized it in 1993 (for fibres and supports), and Varian automated it in 1996 (owing to a special automatic sample-handling system) **(Berka-Zougali et al., 2012).**

The solid phase micro extraction system is relatively straightforward, consisting of only two components : a stainless steel piston and a fiber linked to its end. This fused silica fiber is covered with a polymeric phase and has a thickness of 7 to 100 um.

The SPME is required in a wide number of laboratories in numerous sectors of application, including essential oils, because to its ease and speed of implementation, low cost, availability of many fibers, and especially its automation **(Odeh et al., 2007)**.

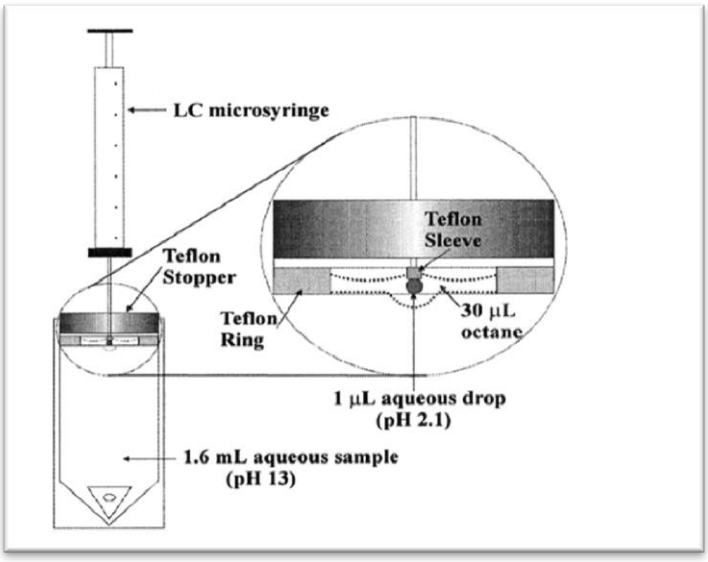


Figure 19: Schematization of Microextraction system **(Ma.,1999).**

Experimental Part

Materials and Methods

I. Material used:

- ♣ Graduated cup (ml).
- ♣ Glass bowl.
- ♣ Saucepan and spoon.
- ♣ Hot plate (heating).
- ♣ Syringe.
- ♣ Electronic balance.
- ♣ Packing boxes
- ♣ Silicone molds.
- ♣ Microwave.
- ♣ Tamis.

II. Méthodes:

Openticia focus indica plup and curcuma based gummies forms were prepared using an old but efficient method of extraction as Swilling in order to extract safely whith a good yield sensitive secondery methabolits like in flowers essential oils, more over when used whith an acid solvent this could be generate more reactive chemical spicies besd on donating proton effect, in addition to more solubility and bioavailebility.

In this purpose, a bed of vegetable butter was used for the solide extraction phase then natural acetic acid for the liquid one, an optimal and safe dose of crud extract or pulp was used for the different formulations with added or free sugar and preservatives.

Ⅱ.1 Formulation of curcuma gummies:

Ⅱ.1.1 Gummies with Turmeric 1: swelling followed by acetic acid extraction:

Table 06: Method of preparation of Gummies with Turmeric form 1, swelling and acetic acid extraction

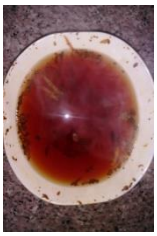
Ingredients and Procedure	Different steps of gummies production
Ingredients: • 50 g of vegetable butter • 10 g of curcuma powder	 

• 5 g of brown sugar • 10 ml of vinegar • 3 g of gelatin sheet Procedure: at first we melt 50g of vegetal butter in a hot water bath under low temperature for 10 min, then we added 10 g of powder curcuma, we let it for 45 minutes then we added 5 g of sugar while stirring constantly. After dissolving the gelatin sheet in water and pouring it on the mixture, we finally got a homogeneous mixture, afterwards using a syringe we picked up the mixture and poured it into silicone molds at room temperature, after four hours of cooling we got gummies as a final result.	     

Ⅱ.1.2 Gummies with turmeric 2: aqueous extraction by microwave:

Table 07 : Method of preparation Gummies with turmeric 2, aqueous extraction by microwave.

Ingredients and Procedure	Different steps of gummies production
Ingredients: • 10 g curcuma (branch) • 500 ml water • 20 g brown sugar • 60 g gelatin powder	 

Procedure: Sample 2: We put 500 ml of water in a bowl with 10 grams of prepared raped curcuma stock, then we added 20 grams of sugar with constant stirring then we put the mixture inside a microwave for 10 minutes to finally get a concentrate of curcuma extract. We added 60 grams of gelatin powder, afterwards using a syringe we picked up the mixture and poured it into silicone molds at room temperature, after four hours of cooling we got gummies as a final result.	        

Ⅱ.1.3 Turmeric Gummies 3: Microwave Aqueous Extraction + Acetic Acid as a Preservative:

Table 08 : Method of preparation Turmeric Gummies 3, Microwave Aqueous Extraction + Acetic Acid as a Preservative.

Ingredients and Procedure	Different steps of gummies production
Ingredients: • 10 g curcuma (branch) • 500 ml water	

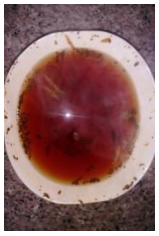
- 20 g brown sugar
- 60 g gelatin powder
- 10 ml vinegar

Procedure:

Sample 3: We put 500 ml of water in a bowl with 10 grams of prepared raped curcuma stock, then we added 20 grams of sugar with constant stirring then we put the mixture inside a microwave for 10 minutes to finally get a concentrate of curcuma extract. We added 60 grams of gelatin powder and add 10 ml of vinegar , afterwards using a syringe we picked up the mixture and poured it into silicone molds at room temperature, after four hours of cooling we got gummies as a result.







Ⅱ.1.4 Turmeric Gummies 4: Extraction by Swelling:

Table 09: method of preparationTurmeric Gummies 4, Extraction by Swelling.

Ingredients and Procedure of preparation	Different steps of gummies production
Ingredients: • 30 g of butter • 3 g curcuma powder • 6 g gelatin powder • 15 g brown sugar Procedure: Sample 4: In a water bath and under low temperature we mixed 30 g of vegetal butter with 3 g of curcuma powder and waited 45 minutes, afterwards we added 15 g of sugar and waited for it to dissolve then added 6 g of gelatin to get the final mixture. as a final step we poured the mixture using syringe into the molds to get the sample 4.	

At last, we got 4 samples as follows:

Figure 20: Curcuma prepared Gummies form.

Ⅱ.2 Preparation of Opuntia ficus-indica fruit gummies:

Ⅱ.2.1 Hendi 1 gummies without added sugar and preservative.

Table 10 : Method of preparation Hendi 1, gummies without added sugar and preservative.

Ingredients and Procedure of preparation	Different steps of gummies production
Ingredients: • 62.5 ml juice of. Opuntia ficus indica • 5g of gelatin. Procedure: Firstly, we add 62.5 ml juice of Opuntia ficus indica and 5g of gelatin in bowl (1). Secondly, We mix the contents with a spoon. Then, we put the mixture into the pot over low heat until dissolved. We let it boil for 15 seconds. We transfer the preparation into the mold and let it rest for 2 hours at room temperature while the preparation is gelling. Finally, we take them out of the mold and put them in a box with a label.	   

Ⅱ.2.2 Hendi 2 gummies with preservative and no added sugar .

Table 11 : method of preparationHendi 2, gummies with preservative and no added sugar.

Ingredients and Procedure of preparation	Different steps of gummies production
Ingredients: • 62.5 ml juice of Opuntia ficus indica. • 5g of gelatin. • 3.75 ml of acid cetric.	 

Procedure: Firstly, we add 62.5 ml juice of Opuntia ficus indica, 5g of gelatin and 3.75 ml of acid cetric with a syringe in bowl (2). Secondly, we mix the contents with a spoon. Then,we put the mixture into the pot over low heat until dissolved. We let it boil for 15 seconds.We transfer the preparation into the mold and let it rest for 2 hours at room temperature while the preparation is gelling. Finally, we take them out of the mold and put them in a box with a label.	  

Ⅱ.2.3 Hendi 3 gummies with preservative and added sugar .

Table 12 : method of preparation Hendi 3, gummies with preservative and added sugar.

Procedure of preparation	**Different steps of gummies production**
Ingredients: • 62.5 ml juice of Opuntia ficus indica • 5g of gelatin • 20g of sugar. • 3.75 ml of acid cetric. Procedure: Firstly, we add 62.5 ml juice of Opuntia ficus indica, 5g of ggelatin, 20g of ssuga and 3.75 ml of acid cetric with a syringe in bowl (3). Secondly, we mix the contents with a spoon. Then, we put the mixture into the pot over	   

low heat until dissolved. We let it boil for 15 seconds. We transfer the preparation into the mold and let it rest for 2 hours at room temperature while the preparation is gelling. Finally, we take them out of the mold and put them in a box with a label.	 

Ⅱ.2.4 Hendi 4 gummies with added sugar and no preservative.

Table 13: Method of preparation Hendi 4, gummies with added sugar and no preservative.

Ingredients and Procedure of preparation	**Different steps of gummies production**
Ingredients: • 62.5 ml juice of Opuntia ficus indica. • 5g of gelatin. • 20g of sugar. Procedure: firstly, we add 62.5 ml juice of Opuntia ficus indica , 5g of gelatin and 20g of sugar in bowl (4). Secondly, we mix the contents with a spoon. Then,we put the mixture into the pot over low heat until dissolved. We let it boil for 15 seconds.We transfer the preparation into the mold and let it rest for 2 hours at room temperature while the preparation is gelling. Finally, we take them out of the mold and put	    

them in a box with a label.	

At last, we got 4 samples as follows :

Figure 21: Opentia Fucus indica prepared gummies form.

Result and Discussion

The quality control of the finished products was carried out by analysing:

- Organoleptic properties,
- Physico-chemical analysis,
- Microbiological quality and stability study by accelerated ageing test,

According to the Algerian official journal **(JORADPN°39 of 02 July 2017)**, Algerian or international standards.

❖ **Result:**

I. Results of analyses of curcuma gummies:

I.1 Turmeric gummies 1: extraction by enfleurage and acetic acid

I. 1. 1 Organoleptic properties:

I D E N T I F I C A T I O N

Product : Turmeric gummies 1.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Aspect	Gelatinous	Sensory
Colour	Yellow	Sensory
Smell	Earthy, characteristic of turmeric.	Sensory
General conclusion :	**In accordance with the product data sheet**.	

I.1.2 Physicochemical analysis

I D E N T I F I C A T I O N

Product : Turmeric gummies 1.	***Date of manufacture: .***
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Solubility Ph Total dry residue Brix	Very good 4.18 30%	Solubilisation in fat and extraction with acetic acid Ph meter Refractometer
General conclusion :	**In accordance with the product data sheet.**	

I .1.3 Microbiological analysis :

I D E N T I F I C A T I O N

Product : Turmeric gummies 1.	***Date of manufacture: .***
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, *halkouma).*
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	Sample					Reference	Standards
	1	2	3	4	5		
Aerobic germs at 30°c*10	3.0	3.2	3.1	2.8	2.9	NA ISO 4833	$r<10^5 <10^6$
Total coliforms	00	00	00	00	00	NA ISO 4831	$r<2<10^2$
Mould	00	00	00	00	00	[ORDER 02/06/2015] O.J. N°48 2015	$r<10<10^2$
Salmonella/25g	Abs	Abs	Abs	Abs	Abs	NA ISO 6579	Abs
GENERAL CONCLUSION :	**Satisfactory result according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**						

Ⅰ.1.4 Stability test :

I D E N T I F I C A T I O N

Product : Turmeric gummies 1.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category :
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	1 control unit at 20-25°c	2 units at 30°c for 21 days	References
Physico-chemical characteristics: - Appearance -pH	No apparent bulging, flaking or leaking defects were found 4.0	No apparent bulging, flaking or leaking defects were found 4.18	NFV
Microbiological	218,33	162	

characteristics: - Microbial flora count /15*10^{-4} mm^2 R-factor	/	0.741	08-402
General conclusion	The product is stable according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).		

Ⅰ.2 Turmeric Gummies 2: Aqueous microwave extraction

Ⅰ.2.1 Organoleptic properties

I D E N T I F I C A T I O N

Product : Turmeric gummies 2.	*Date of manufacture:* .
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Aspect Colour Smell	Gelatinous Yellow Earthy, characteristic of turmeric.	Sensory Sensory Sensory
General conclusion :	**In accordance with the product data sheet.**	

Ⅰ.2.2 Physicochemical analysis

I D E N T I F I C A T I O N

Product : Turmeric gummies 2.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Solubility Ph Total dry residue Brix	Good 5.4 17%	Mixing in water and microwave extraction Ph meter Refractometer
General conclusion :	In accordance with the product data sheet	

Ⅰ.2.3 Microbiological analysis ;

I D E N T I F I C A T I O N

Product : Turmeric gummies 2.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	Sample					Reference	Standards
	1	2	3	4	5		
Aerobic germs at 30°c*10	5.0	5.5	5.3	5.2	5.1	NA ISO 4833	$r<10^5<10^6$
Total coliforms	00	00	00	00	00	NA ISO 4831	$r<2<10^2$
Mould	00	00	00	00	00	[ORDER 02/06/2015] O.J. N°48 2015	$r<10<10^2$
Salmonella/25g	Abs	Abs	Abs	Abs	Abs	NA ISO 6579	Abs
GENERAL CONCLUSION :	**Satisfactory result according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**						

Ⅰ.2.4 Stability test:

I D E N T I F I C A T I O N

Product : Turmeric gummies 2.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category :
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	1 control unit at 20-25°c	2 units at 30°c for 21 days	References
Physico-chemical characteristics: -Appearance -pH	No apparent bulging, flaking or leaking defects were found 5.3	No apparent bulging, flaking or leaking defects were found 5.4	NFV 08-402
Microbiological characteristics: -Microbial	250,45	210, 33	

flora count /15*10^{-4} mm^2 R-factor	/	0.839	
General conclusion	**The product is stable according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**		

Ⅰ.3 Turmeric Gummies 3: aqueous microwave extraction + acetic acid as preservative

Ⅰ.3.1 Organoleptic properties

I D E N T I F I C A T I O N .

Product : Turmeric gummies 2.	Date of manufacture: .
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Aspect	Gelatinous	Sensory
Colour	Yellow	Sensory
Smell	Earthy, characteristic of turmeric.	Sensory.
General conclusion :	**In accordance with the product data sheet.**	

I.3.2 Physicochemical analysis

I D E N T I F I C A T I O N

Product : Turmeric gummies 3.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Solubility Ph Total dry residue Brix	Very good 4.52 28%	Water mixing and microwave extraction Ph meter Refractometer .
General conclusion :	In accordance with the product data sheet.	

I.3.3 Microbiological analysis

I D E N T I F I C A T I O N

Product : Turmeric gummies 3.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	Sample					Reference	Standards
	1	2	3	4	5		
Aerobic germs at 30°c*10	2.2	1.9	2.0	2.1	1.8	NA ISO 4833	$r<10^5<10^6$
Total coliforms	00	00	00	00	00	NA ISO 4831	$r<2<10^2$
Mould*10	05	06	02	04	03	[ORDER 02/06/2015] O.J. N°48 2015	$r<10<10^2$
Salmonella/25g	Abs	Abs	Abs	Abs	Abs	NA ISO 6579	Abs
GENERAL CONCLUSION :	**Satisfactory result according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**						

I.3.4 Stability test

I D E N T I F I C A T I O N

Product : Turmeric gummies 3.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category :
Nature of packaging: Food.	

A N A L Y S E S

Analyses carried out	1 control unit at 20-25°c	2 units at 30°c for 21 days	References
Physico-chemical characteristics: -Appearance -pH	No apparent bulging, flaking or leaking defects were found 4.4	No apparent bulging, flaking or leaking defects were found 4.52	NFV 08-402
Microbiological characteristics: -Microbial flora count /15*10^{-4} mm^2	145,6	138, 5	

R-factor	/	0.952	
General conclusion	**The product is stable according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**		

I.4 Turmeric gummies 4: enfleurage extraction

I.4.1 Organoleptic properties

I D E N T I F I C A T I O N .

Product : Turmeric gummies 4.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Aspect	Gelatinous	Sensory
Colour	Yellow	Sensory
Smell	Earthy, characteristic of turmeric.	Sensory
General conclusion :	**In accordance with the product data sheet.**	

I.4.2 Physicochemical analysis

I D E N T I F I C A T I O N

Product : Turmeric gummies 4.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Solubility Ph Total dry residue Brix	Very good 4.16 28%	Mixing with fat Ph meter Refractometer
General conclusion :	In accordance with the product data sheet.	

I.4.3 Microbiological analysis :

I D E N T I F I C A T I O N

Product : Turmeric gummies 4.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	Sample					Reference	Standards
	1	2	3	4	5		
Aerobic germs at 30°c*10	1.5	1.7	1.6	2.0	1.9	NA ISO 4833	$r<10^5<10^6$
Total coliforms	00	00	00	00	00	NA ISO 4831	$r<2<10^2$
Mould*10	04	01	06	04	05	[ORDER 02/06/2015] O.J. N°48 2015	$r<10<10^2$
Salmonella/25g	Abs	Abs	Abs	Abs	Abs	NA ISO 6579	Abs
GENERAL CONCLUSION :	**Satisfactory result according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**						

I.4.4 Stability test

I D E N T I F I C A T I O N

Product : Turmeric gummies 4.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category :
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	1 control unit at 20-25°c	2 units at 30°c for 21 days	References
Physico-chemical characteristics: -Appearance -pH	No apparent bulging, flaking or leaking defects were found 4	No apparent bulging, flaking or leaking defects were found 4.16	NFV 08-402
Microbiological characteristics: -Microbial flora count /15*10^{-4} mm^2	205,5	190,4	

R-factor	/	0.926	
General conclusion :	**The product is stable according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**		

II. Results of analyses of Opuntia ficus indica fruit gummies:

Ⅱ.1 Hendi 1 Gummies with no added sugar and no preservatives

Ⅱ.1.1 Organoleptic properties

I D E N T I F I C A T I O N

Product: Gummies at Hendi 1.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Aspect	Gelatinous	Sensory
Colour	orange	Sensory
Smell	Fruity, characteristic of Hendi.	Sensory.
General conclusion :	**In accordance with the product data sheet.**	

Ⅱ.1.2 Physicochemical analysis

I D E N T I F I C A T I O N

Product: Gummies at Hendi 1.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Ph Total dry residue Brix	3.67 21%	Ph meter Refractometer
General conclusion :	In accordance with the product data sheet.	

Ⅱ.1.3 Microbiological analysis :

I D E N T I F I C A T I O N

Product: Gummies at Hendi 1.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	Sample					Reference	Standards
	1	2	3	4	5		
Aerobic germs at 30°c*10	4.0	4.2	4.1	4.3	4.1	NA ISO 4833	$r<10^5<10^6$
Total coliforms	00	00	00	00	00	NA ISO 4831	$r<2<10^2$
Mould*10	00	00	00	00	00	[ORDER 02/06/2015] O.J. N°48 2015	$r<10<10^2$
Salmonella/25g	Abs	Abs	Abs	Abs	Abs	NA ISO 6579	Abs
GENERAL CONCLUSION :	**Satisfactory result according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**						

Ⅱ.1.4 Stability test:

I D E N T I F I C A T I O N

Product: Gummies at Hendi 1.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category :
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	1 control unit at 20-25°c	2 units at 30°c for 21 days	References
Physico-chemical characteristics: -Appearance -pH	No apparent bulging, flaking or leaking defects were found 3.5	No apparent bulging, flaking or leaking defects were found 3.67	NFV 08-402
Microbiological characteristics: -Microbial	293,9	250,8	

flora count /15*10^{-4} mm^2 R-factor	/	0.853	
General conclusion :	**The product is stable according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**		

Ⅱ.2 Hendi 2 gummies with preservative and no added sugar :

Ⅱ.2.1 Organoleptic properties

I D E N T I F I C A T I O N

Product: Gummies at Hendi 2.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Aspect	Gelatinous	Sensory
Colour	orange	Sensory
Smell	Fruity, characteristic of Hendi.	Sensory
General conclusion :	**In accordance with the product data sheet**	

Ⅱ.2.2 Physicochemical analysis

I D E N T I F I C A T I O N

Product: Gummies at Hendi 2.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Ph Total dry residue Brix	3.5 18%	Ph meter Refractometer
General conclusion :	In accordance with the product data sheet	

Ⅱ.2.3 Microbiological analysis :

I D E N T I F I C A T I O N

Product: Gummies at Hendi 2.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	Sample					Reference	Standards
	1	2	3	4	5		
Aerobic germs at 30°c*10	6.0	6.7	7.5	6.9	7.3	NA ISO 4833	$r<10^5<10^6$
Total coliforms	00	00	00	00	00	NA ISO 4831	$r<2<10^2$
Mould*10	00	00	00	00	00	[ORDER 02/06/2015] O.J. N°48 2015	$r<10<10^2$
Salmonella/25g	Abs	Abs	Abs	Abs	Abs	NA ISO 6579	Abs
GENERAL CONCLUSION :	**Satisfactory result according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**						

Ⅱ.2.4 Stability test :

I D E N T I F I C A T I O N

Product: Gummies at Hendi 2.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category :
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	1 control unit at 20-25°c	2 units at 30°c for 21 days	References
Physico-chemical characteristics: -Appearance	No apparent bulging, flaking or leaking defects were found	No apparent bulging, flaking or leaking defects were found	NFV 08-402
-pH	3.2	3.5	
Microbiological characteristics: -Microbial flora count /$15*10^{-4}$ mm^2	300,6	310	

R-factor	/	0.969	
General conclusion :	**The product is stable according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**		

Ⅱ.3 Hendi 3 gummies with preservatives and added sugar :

Ⅱ.3.1 Organoleptic properties :

I D E N T I F I C A T I O N

Product: Gummies at Hendi 3.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Aspect	Gelatinous	Sensory
Colour	orange	Sensory
Smell	Fruity, characteristic of Hendi.	Sensory
General conclusion :	In accordance with the product data sheet	

Ⅱ.3.2 Physicochemical analysis

I D E N T I F I C A T I O N

Product: Gummies at Hendi 3.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Ph Total dry residue Brix	3.35 32%	Ph meter Refractometer
General conclusion :	In accordance with the product data sheet.	

Ⅱ.3.3 Microbiological analysis :

I D E N T I F I C A T I O N

Product: Gummies at Hendi 3.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	Sample					Reference	Standards
	1	2	3	4	5		
Aerobic germs at 30°c*10	4.2	4.5	4.8	5.2	4.9	NA ISO 4833	$r<10^5<10^6$
Total coliforms	00	00	00	00	00	NA ISO 4831	$r<2<10^2$
Mould*10	00	00	00	00	00	[ORDER 02/06/2015] O.J. N°48 2015	$r<10<10^2$
Salmonella/25g	Abs	Abs	Abs	Abs	Abs	NA ISO 6579	Abs
GENERAL CONCLUSION :	**Satisfactory result according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**						

II.3.4 Stability test :

I D E N T I F I C A T I O N

Product: Gummies at Hendi 3.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category :
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	1 control unit at 20-25°c	2 units at 30°c for 21 days	References
Physico-chemical characteristics: -Appearance -pH	No apparent bulging, flaking or leaking defects were found 3.2	No apparent bulging, flaking or leaking defects were found 3.35	NFV 08-402
Microbiological characteristics: -Microbial	275,3	287,6	

flora count /15*10^{-4} mm^2 R-factor	/	0.957	
General conclusion :	**The product is stable according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**		

Ⅱ.4 Hendi 4 gummies with added sugar and no preservatives:

Ⅱ.4.1 Organoleptic properties :

I D E N T I F I C A T I O N

Product: Gummies at Hendi 4.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Aspect Colour Smell	Gelatinous orange Fruity, characteristic of Hendi.	Sensory Sensory Sensory
General conclusion :	**In accordance with the product data sheet.**	

Ⅱ.4.2 Physicochemical analysis :

I D E N T I F I C A T I O N

Product: Gummies at Hendi 4.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	**Results**	**Methods**
Ph Total dry residue Brix	3.57 32%	Ph meter Refractometer
General conclusion :	In accordance with the product data sheet	

Ⅱ.4.3 Microbiological analysis:

I D E N T I F I C A T I O N

Product: Gummies at Hendi 4.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category : Other confectionery products (caramels, sweets, nougats, halkouma).
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	Sample					Reference	Standards
	1	2	3	4	5		
Aerobic germs at 30°c*10	3.5	3.0	3.9	3.1	3.7	NA ISO 4833	$r<10^5<10^6$
Total coliforms	00	00	00	00	00	NA ISO 4831	$r<2<10^2$
Mould*10	00	00	00	00	00	[ORDER 02/06/2015] O.J. N°48 2015	$r<10<10^2$
Salmonella/25g	Abs	Abs	Abs	Abs	Abs	NA ISO 6579	Abs
GENERAL CONCLUSION :	**Satisfactory result according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**						

Ⅱ.4.4 Stability test :

I D E N T I F I C A T I O N

Product: Gummies at Hendi 4.	**Date of manufacture: .**
Nature of the product : Gelatin.	Product category :
Nature of packaging: Food.	/

A N A L Y S E S

Analyses carried out	1 control unit at 20-25°c	2 units at 30°c for 21 days	References
Physico-chemical characteristics: -Appearance -pH	No apparent bulging, flaking or leaking defects were found 3.5	No apparent bulging, flaking or leaking defects were found 3.57	NFV 08-402
Microbiological characteristics: -Microbial flora count /15*10^{-4} mm^2	298,1	320,65	

R-factor	/	0.932	
General conclusion	**The product is stable according to the interministerial decree of 04 October 2016 fixing the microbiological criteria for foodstuffs (JORADPN°39 of 02 July 2017).**		

❖ **Discussion**

Formulation:

The obtained gummy form is practical and very suitable for adults as well as children, it contains an efficient non-toxic dose of therapeutic natural agents, different reciepies were tested in order to study the quality controle and stability of the final products

Quality controle and stability:

- All obtained forms were tested according to national standards, which gave satisfactory results and are suitable to be produced and commercialized in local market, which dosn't need sanitary insurance according to the CNPM.
- We also observed that preservatives and sugar are not needed in case of natural fruit pulp and curcuma.
- And are stable at least for 15 days at room temperature < 20°.
- Otherwise, tested formulations could be more optimized for better organoleptic proprieties as tast, texture…

Ⅰ. SAR and the synergic Effect of Isorhamnetin:

Ⅰ.1 The major secondary metabolites of Opuntia ficus indica:

Isorhamnetin is a flavonoid component with many biological activities such as antioxidant, anti-inflammatory, and anticancer

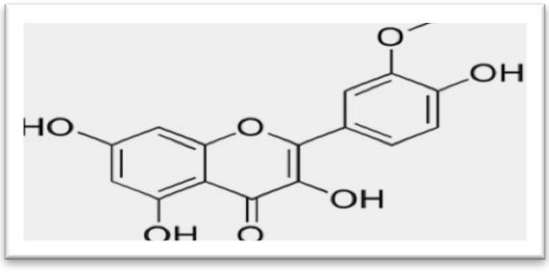


Figure 22: Figure: Chemical structure of isorhamnetin **(Gong et al.,2020)**

Isorhamnetin has been proven in studies to have a wide range of pharmacological effects on cardiovascular illnesses **(Zhao et Liu.,2008)** and a variety of malignancies **(Li et al .,2011)**, as well as the ability to protect neurological diseases like Alzheimer's disease **(Ishola et al .,2019)** It also exhibits anti-hyperuricemia **(Adachi et al.,2019)** and anti-pulmonary fibrosis (Zheng et al.,2019) pharmacodynamics. Isorhamnetin's pharmacological actions are linked to its control of the NF-B, PI3K/AKT, MAPK, and other signaling pathways, as well as their downstream components. Isorhamnetin's pharmacological activity and mechanism are now being studied in depth **(Gong et al.,2020).**

Isorhamnetin has been found to be cytotoxic to H9C2 cardiomyocytes **(Dong et al.,2015)** and mouse primary hepatocytes **(Liang et al.,2017)**, as well as causing DNA damage in HepG2 cells **(Zhang et al.,2015).**

Ⅰ.2 Cardio-cerebrovascular and nerve protection:

Cardiovascular and cerebrovascular disorders are on the rise, and they are putting a huge financial strain on countries around the world. Cardiovascular problems are more likely to cause major illnesses. Atherosclerosis, for example, causes myocardial fibrosis, which eventually leads to heart failure. Anti-atherosclerosis, endothelial cell protection, anti-myocardia ischemia, anti-hypotension, anti-hypoglycemia, and antithrombosis are among the many preventative and therapeutic actions of isorhamnetin on cardiovascular and cerebrovascular illnesses. Isorhamnetin's cardiovascular-protective actions are nearly entirely due to its antioxidation, anti-inflammation, and anti-apoptosis capabilities. Isorhamnetin can also help with nerve function, cognition, and memory, as well as prevent and treat neurodegenerative diseases **(Gong et al.,2020).**

By influencing the PI3K/AKT and NF-B signaling pathways, isorhamnetin can protect cardiovascular cells from inflammation, oxidative damage, and apoptosis **(Gong et al., 2020).**

Figure 23 shows the mechanism of action of isorhamnetin against cardiovascular and cerebrovascular diseases.

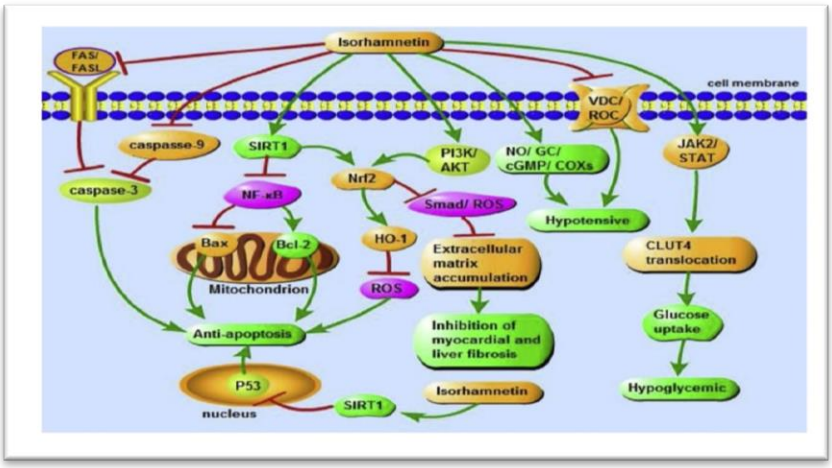


Figure 23: Mechanism of action of isorhamnetin against cardiovascular and cerebrovascular diseases. **(Gong et al.,2020).**

I.3 Anti-tumor:

Isorhamnetin inhibits human cervical cancer cells **(Yang et al.,2003);(Wei et al.,2018)**, lung cancer cells **[Li et al.,2012);(Ruan et al.,2015)**, colon cancer cells **(Antunes et al.,2014);(Sara et al.,2010)**, breast cancer cells **[(Hu et al.,2019);(Hu et Deng .,2013),** pancreatic cancer cells **(Wang et al.,2018)**, nasopharyngeal cancer cells **(Luo et al.,2011)**, liver cancer cells **(Jiang et al.,2012)**, gastric cancer cells **(Li et al.,2008)**, and other cancer cells. Isorhamnetin suppresses tumor cell growth, promotes apoptosis, and controls tumor suppressor genes, proto-Oncogenes, and signal pathways **(Li et al .,2011).**

Figure 24 shows the anti-tumor mechanism of isorhamnetin

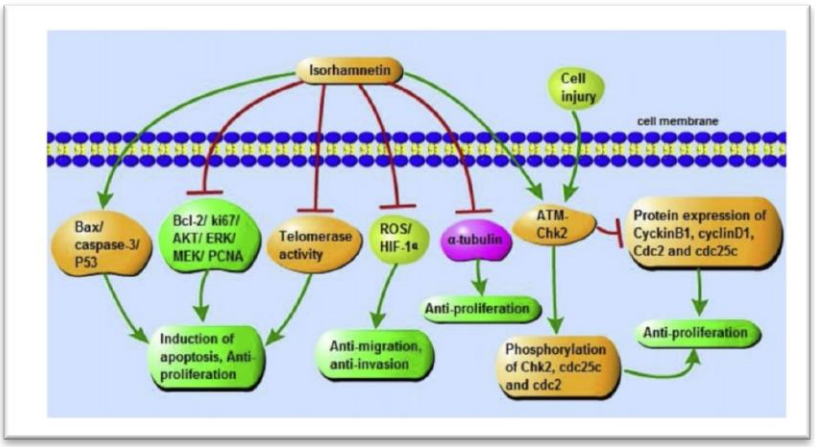


Figure 24: The anti-tumor mechanism of isorhamnetin. Isorhamnetin inhibits tumor cell proliferation and promotes apoptosis by regulating the expression of tumorrelated genes or proteins such as Bcl-2 and Bax **(Gong et al.,2020).**

Ⅰ.4 Effect on hepatocytes :

Isorhamnetin inhibits ConA-induced acute fulminant hepatitis (AFH) in rats via decreasing apoptosis and autophagy **(Lu et al.,2018).** It protects human normal hepatocytes (LO2) against paracetamol (APAP)-induced damage by decreasing MDA content, increasing GSH content, increasing SOD and GSH-Px activity, and lowering ALT and AST release **(Jiang et al.,2018).**

However, the exact mechanism of action is unknown and requires additional investigation.

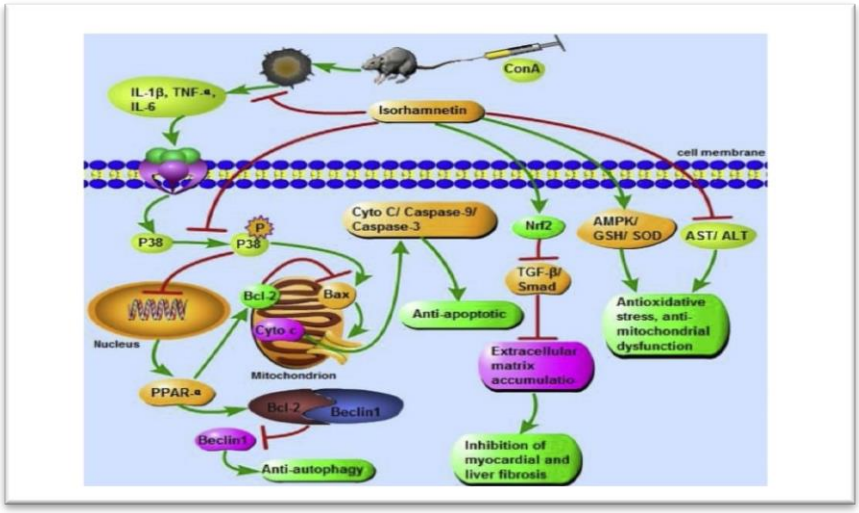


Figure 25: Protective mechanism of isorhamnetin on liver. Isorhamnetin can protect the liver from many injuries such as autophagy and aoptosis by regulating a variety of signal pathways **(Gong et al.,2020).**

Ⅰ.5 Prevention of obesity:

In 3T3-L1 cells, isorhamnetin-mediated mitochondrial biogenesis and AMPK activation are involved in the molecular mechanism of action **(Mak-Soon et Yangha.,2018).**

Isorhamnetin's mitochondrial biogenic action in adipocytes could be linked to increased mitochondrial gene expression, mtDNA replication, and AMPK activation **(Gong et al.,2020).**

Figure 26 shows the obesity-preventing mechanism of isorhamnetin.

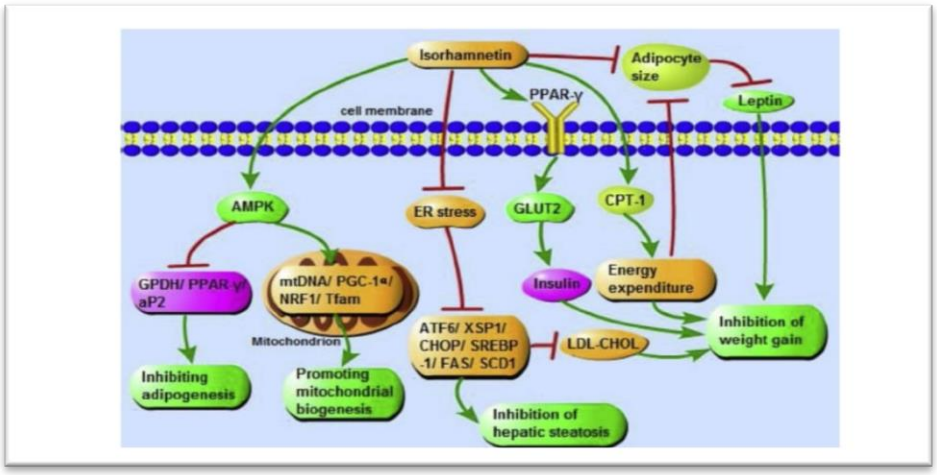


Figure 26: Obesity-preventing mechanism of isorhamnetin. Isorhamnetin can prevent obesity by inhibiting adipogenesis and promoting mitochondrial biogenesis **(Gong et al., 2020).**

I.6 Isorhamnetin and Kaempferol synergetic effect:

Figure 27 wihch presents the HPLC profile of Opentia Ficus Indica, indicates a probability of synergetic effect between majoritary compounds and minor ones that have structural affinity by retention time as: compound 3 kaempferol-3-O-rutinoside; (4) isorhamnetin-3-O-rutinoside (retention time, 41.02 min) via hydrogen bonds, combining by the way their proprieties to guive a better controlled synergetic therapeutic effect, possibly by the presence of glucoside moity which improuve solubility, digestibility and transport of the the active compounds to target cells active site.

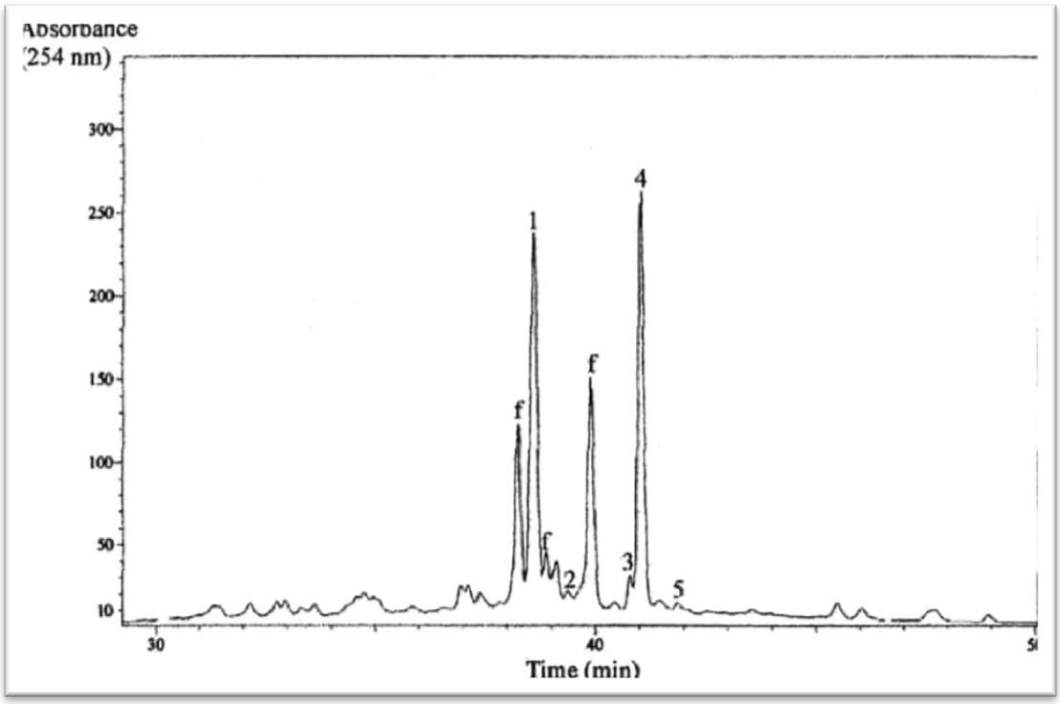


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Figure 27: HPLC profile at 254 nm of O. ficus indica whole fruit juice. (1) Probably isorhamnetin triglycoside (retention time, 38.61 min); (2) rutin; (3) kaempferol-3-O-rutinoside; (4) isorhamnetin-3-O-rutinoside (retention time, 41.02 min); (5) isorhamnetin-3-O-glucoside; and (f) flavonol glycoside **(Galati et al.,2003)**

Ⅰ.7 Kaempferol:

Kaempferol is a natural flavonoid compound widely found in tea, broccoli, cabbage, and other plants **(Chen & Chen, 2013) (Li.,2020)**

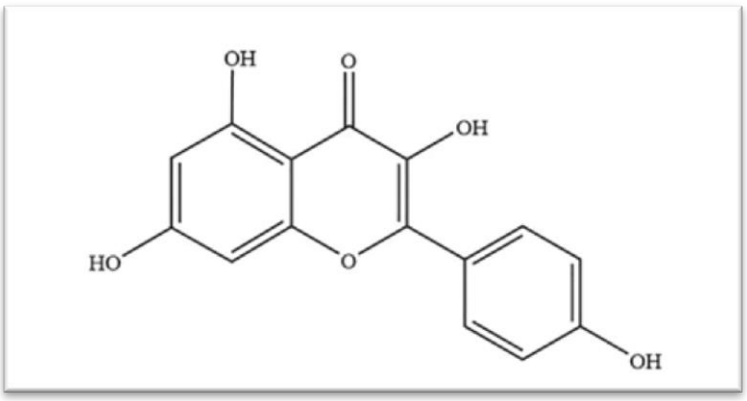


Figure 28: The structure of Kaempferol **(Li.,2020).**

Intake of Kaempferol -rich foods has been shown in studies to lessen the risk of disorders including hyperlipidemia and cardiovascular disease. According to clinical research, certain Kaempferol glycosides show antioxidant and anti-inflammatory properties **(Calderon-Montano, Burgos-Morón, PérezGuerrero, & López-Lázaro, 2011) (Li.,2020)**

Ⅰ.8 Protective effects of kaempferol against reactive oxygen species(ROS)-induced hemolysis:

It is well acknowledged that the peroxidation of membranes induced by ROS is one of the primary events in the cellular oxidative damage . Erythrocyte served as a model to study the lipid peroxidation because of their high content of polyunsaturated fatty acid. The inhibition of hemolysis reached 95.21%after treatment with 100 mg/mL of kaempferol, indicating that kaempferol could significantly attenuated the ROS-induced oxidative hemolysis in a dose dependent manner **(Liao et al.,2016)**

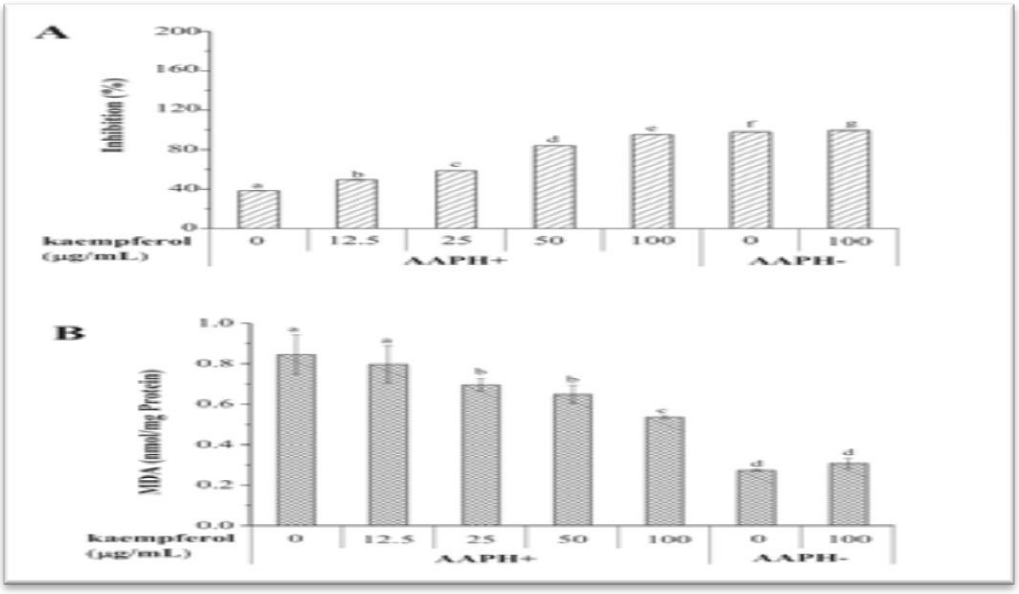


Figure 29:(A) The inhibition of erythrocyte hemolysis treated with kaempferol (12.5e100 mg/mL) for 30 min and 200 mM AAPH; (B) The MDA content in the erythrocytes pre-cultured with different concentrations of kaempferol (12.5e100 mg/mL) for 20 min and treated with 200 mM AAPH for 2 h **(Liao et al.,2016).**

I.9 Kaempferol inflammatory :

The in vivo studies showed that kaempferol could improve the recovery of hindlimb motor function and ameliorate tissue damage in the spinal cord after SCI. Moreover, administration of kaempferol reduced microglia activation and oxidative stress level in the spinal cord. The in vitro studies showed that kaempferol suppressed the microglia activation resulting from the administration of LPS with ATP to BV-2 cells. Pretreated BV2 cells with kaempferol reduced the generation of reactive oxygen species (ROS) by inhibiting NADPH oxidase 4, and then, suppressed the phosphorylation of p38 MAPK and JNK, which subsequently inhibited nuclear translocation of NF-κB p65 to express pro-inflammatory factors. We also observed that kaempferol could inhibite the pyroptosis related proteins (NLRP3 Caspase-1 p10 ASC N-GSDMD) and reduce the release of IL-18 and IL-1β. In conclusion, kaempferol was able to reduce oxidative stress and inflammatory response through down-regulation of ROS dependent MAPKs- NF-κB and pyroptosis signaling pathway, which suggested that kaempferol might be a novel promising therapeutic agent for SCI. **(Liu et al.,2021)**

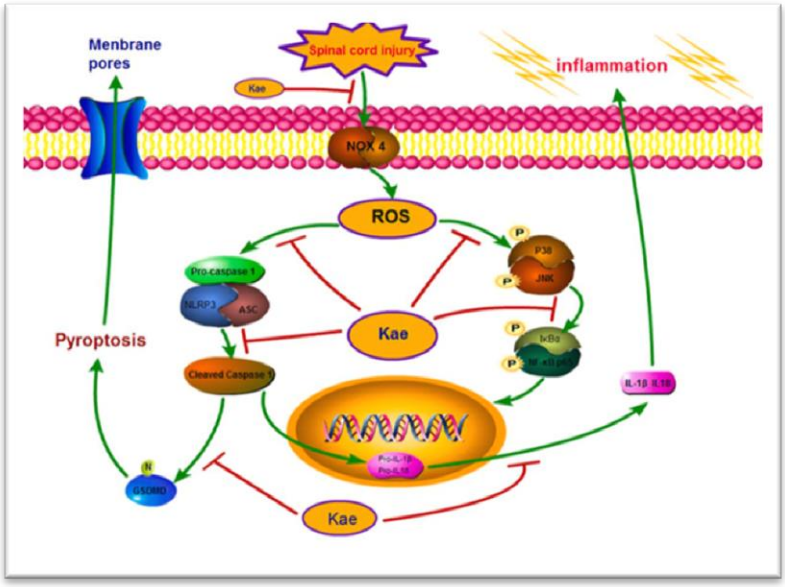


Figure 30: Kaempferol action Mechanism **(Liu et al.,2021)**.

Ⅱ. The SAR and Synergistic Effect of Curcumin Combination Chemotherapy:

Ⅱ.1 Synergistic effect of curcumin and its analogs on anticancer activity:

On prostate cancer cell lines, the synergistic activity of multiple carotenoids like lycopene, phytoene, and phytofluene, or carotenoids and polyphenols like carnosic acid and curcumin, and/or other substances like vitamin E was tested. This combination synergistically inhibits /sthe androgen receptor activity and demonstrated 4-fold higher activity on /sElectrophile/Antioxidant Response Element (EpRE/ARE) system /sthan the sum of the activities of the single constituents. The synergistic effect was also reported when curcumin, vitamin E, and tomato extract were combined rather than each pair of components separately **(Linnewiel-Hermoni et al.,2015) (Hosseini-Zare et al.,2021)**

Curcumin enhanced the anticancer activity of 5-fluorouracil plus cisplatin (5-FP) in human gastric cell lines by reducing cell viability, inhibiting colony formation, and inducing apoptosis by caspase-3/-8 activation, Bcl-2 downregulation, and Bax overexpression.It's worth noting that low dose 5-FP boosted curcumin efficacy more than high dose 5-FP, implying a synergetic impact of curcumin and 5-FP**.(Yin et al.,2019) (Hosseini-Zare et al.,2021)**

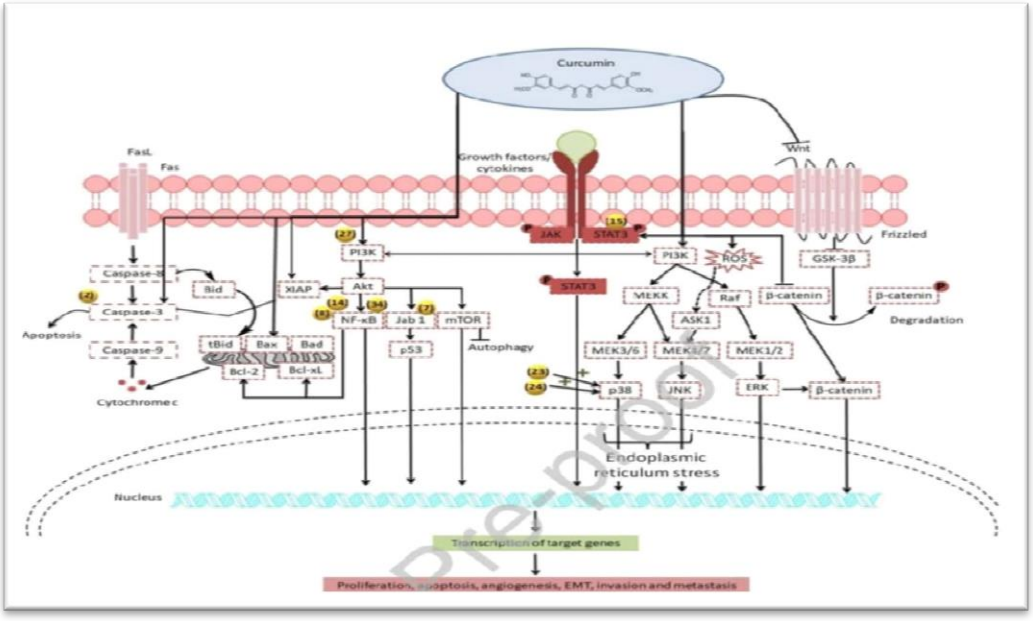


Figure 31: Schematic representation of multiple anticancer mechanisms of distinct analogues of curcumin. **(Sethi et al., 2021).**

Ⅱ.2 Synergistic effect of curcumin on antioxidant activity:

Antioxidants must be consumed because the body cannot produce them. Curcumin or its analogs, in combination with other therapeutic agents, have recently been demonstrated to have good antioxidant action. Piperine increases medication bioavailability by inhibiting glucuronidation in the liver and small intestine. Curcumin bioavailability was improved, and neurotoxicity and extrapyramidal side effects of haloperidol were reduced in the rat brain after co-administration of curcumin and piperine**. (Bishnoi et al., 2011) (Hosseini-Zare et al., 2021)**

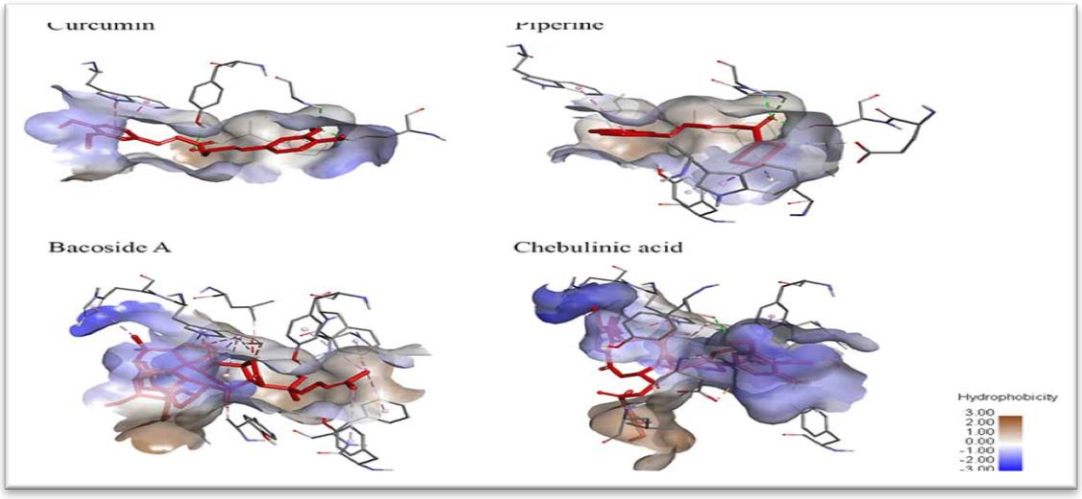


Figure 32: Curcumin and piperine **(Abdul Manap et al.,2019).**

Ⅱ.3 Curcumin's molecular and cellular targets:

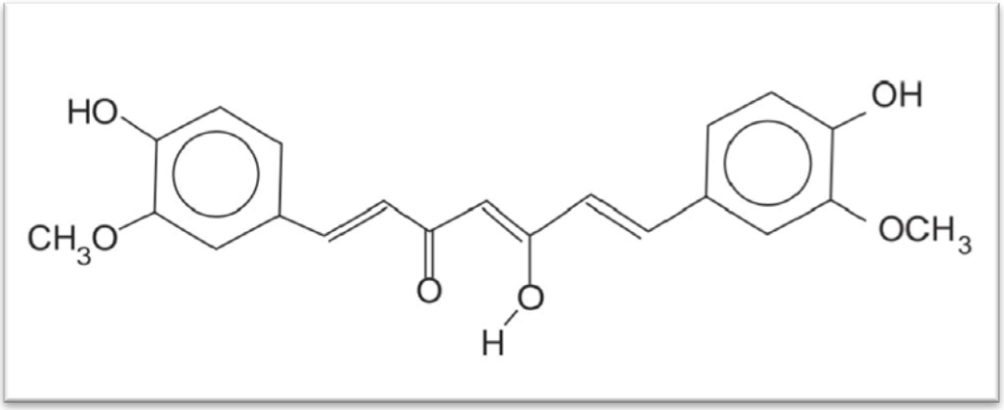


Figure 33: Chemical structure of curcumin **(BERNARD et al.,2005).**

The enormous number of papers on curcumin's biological activities throughout the years demonstrate how diverse they are, impacting a wide range of cellular functions **(Sharma et al., 2005)**.

NFkB (nuclear factor kB), a nuclear factor that governs the expression of several genes implicated in these events **(Cynober et al.,2005)**, is one of the most studied pathways that controls numerous cellular processes (cell proliferation, apoptosis, inflammatory or autoimmune response). Curcumin suppresses the NFkB pathway by decreasing the activity of the IKKs complex (IkB kinases) responsible for IkB phosphorylation, according to several research **(Aggarwal et al.,2003 ;Woo et al.,2005)** on various cell types. IkB is no longer phosphorylated, but it is still linked with NFkB, blocking the latter's translocation into the core. Curcumin, on the other hand, suppresses transcription factors such as AP-1 (activator protein 1), which is required for cell proliferation, and Egr-1 (early growth response 1), which is a very early effector in the cell differentiation cascade **(Aggarwal et al.,2003 ;Woo et al.,2005 ;Cho et al.,2005)**.It also inhibits mitogen-activated protein kinases (MAPKinases), such as c-Jun N-terminal kinase (JNK) **(Chen et al.,1998)** and other kinases, such as protein kinase C (PKC) , which control inflammation, apoptosis, and oncogenesis **(Aggarwal et al.,2003 ; Jobin et al.,1999 ; Woo et al.,2005 ; Cho et al.,2005).**

Lipooxygenase (LOX), NO synthase (NOS), type 9 metalloproteinases (MMP-9), uPA, tumor necrosis factor (TNF), and different chemokines are all inhibited by curcumin and its derivatives **(Aggarwal et al.,2003 ;Shishodia et al.,2003 ;Woo et al.,2005 ;Cho et al.,2005).** It also inhibits the expression of cyclooxygenases type 2 (COX-2) **(Lee et al., 2005 ;Plummer et al.,1999 ; Shishodia et Al.,2003 ;Cho et al.,2005)** which helps to explain its anti-carcinogenic and anti-inflammatory properties.

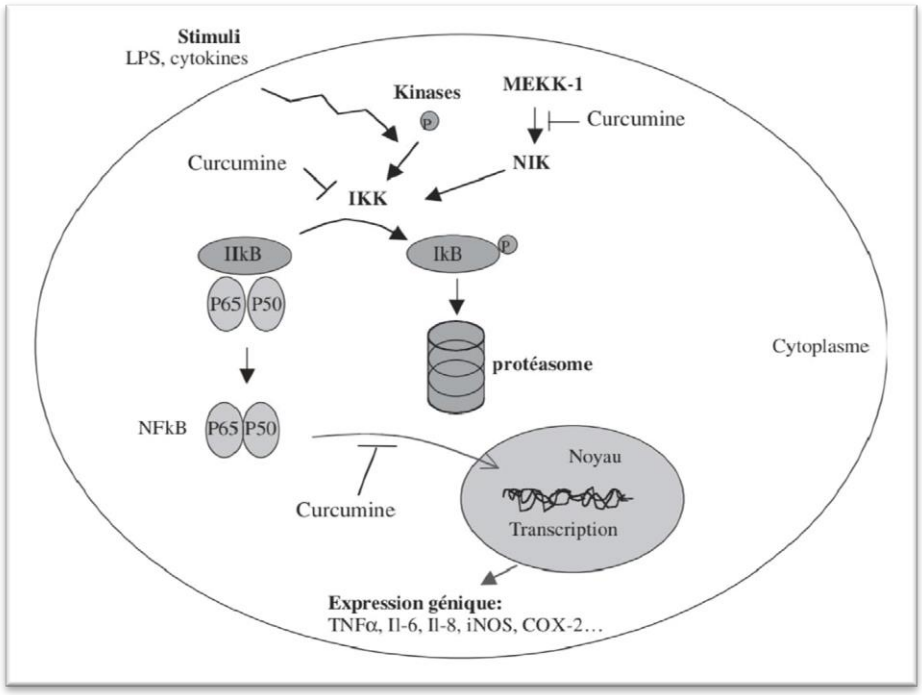


Figure 34: Curcumin's effect and the action of NF-kB are described in simple Terms **(Cynober et al.,2005)**.

The stimulation of transcription of several genes, including TNF, Il-6, Il-8, iNOS, and COX-2, is caused by the translocation of NF-kB into the nucleus and its binding to DNA on its target sequences. The two NF-kB subunits [p65 and p50] are released from the IkB connection during this translocation, inhibiting NF-kB activation. IkB is phosphorylated by IKK [IkB kinase], which is activated by other kinases, after stimulation [LPS, cytokines], causing the connection between IkB and NF-kB to be broken and IkB to be degraded. Curcumin inhibits NF-kB DNA binding, IKK activation, and IkB phosphorylation, resulting in a potent inhibitory effect on NF-kB-controlled pathways. IkB : NF-kB inhibitor, IKK : IkB kinase, NIK : NF-kB inducing kinase, MEKK : Mitogen-activated protein kinase kinase kinase kinase 1, LPS : lipopolysaccharide, TNF : tumor necrosis factor, IL : interleukin, iNOS : inducible c oxide syntha **(BERNARD et al.,2005)**.

Curcumin's cytotoxic activity and ability to induce apoptosis in several cancer cell lines are two of its most recognized effects, making it a potentially attractive anti-cancer agent. Curcumin suppresses cell proliferation and stops the cycle of cells from a variety of malignancies, including colon, breast, kidney, prostate, melanoma, lymphoid, myeloid, and

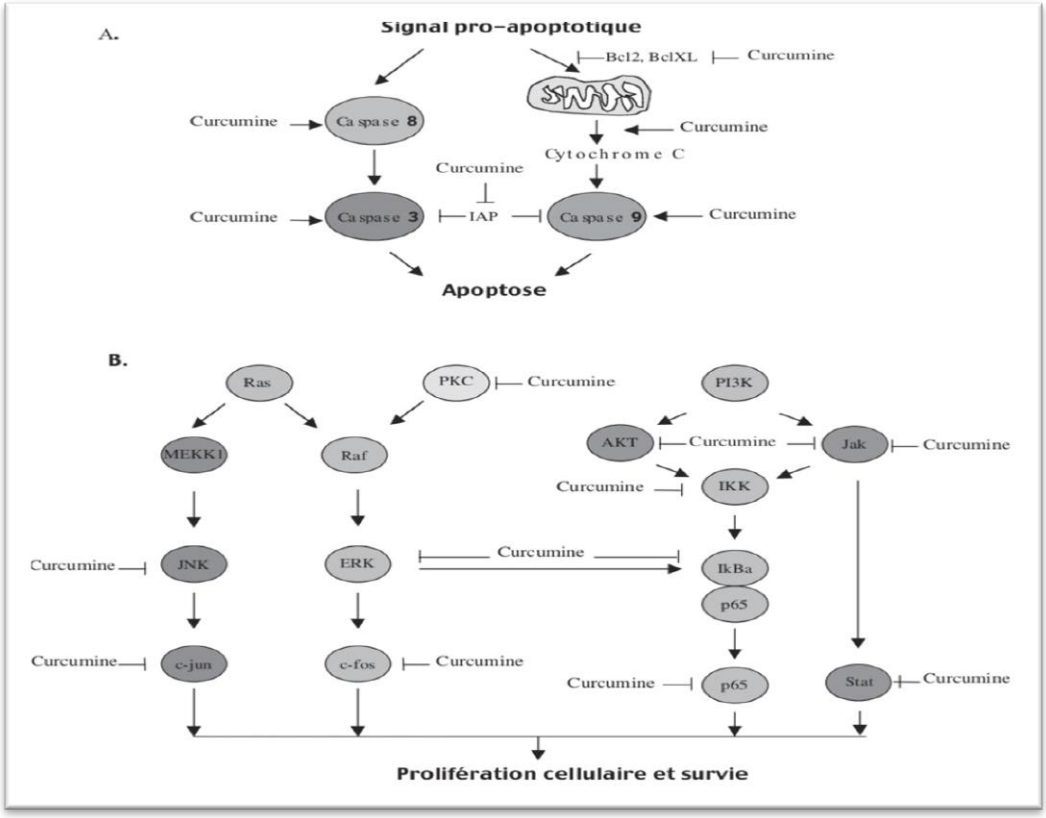
epithelial tumors **(Kelloff et al.,2000 ;Sharma et al.,2005 ; Aggarwal et al.,2003 ;Lee et al.,2005 ;Plummer et al.,1999 ; Siwak et al.,2005 ;Anto et al.,1996)** processes can explain its impact on the cell cycle and apoptosis. Curcumin inhibits the expression of cyclines D1 via stimulation of PPAR- (proliferatoractivated-receptor-), inhibits the induction of ornithine decarboxylase (ODC), inhibits the expression of COX-2, induces apoptosis by inhibiting the expression of Bcl-2 and Bcl-xl and increasing the stability of p53, the generation of reactive oxygen species (ROS), the release of cytochrome **(Kelloff et al.,2000 ; Sharma et al.,2005 ; Aggarwal et al.,2003 ; Siwak et al.,2005 ;Anto et al.,1996 ;Fullbeck et al.,2005).**

Curcumin's interaction with NFkB, Akt/ PK B, AP-1, or JNK has also been proposed to explain its antitumor effects **(Sharma et al.,2005 ; Aggarwal et al.,2003 ;Lee et al.,2005 ;Plummer et al.,1999 ;Siwak et al.,2005 ;Anto et al.,1996).**

Curcumin has been proven to inhibit carcinogenesis and may be a good cancer chemopreventive agent **(Kelloff et al.,2000 ;Sharma et al.,2005 ; Aggarwal et al.,2003 ;Anto et al.,1996)** Curcumin appears to prevent the initiation and promotion phases of carcinogenesis, particularly in cancer models of the colon and skin **(Sharma et al.,2005 ;Conney et al.,2003).** This anti-mutagenesis activity can be attributed to a variety of mechanisms, including suppression of the proinflammatory arachidonic pathway, ODC (ornithine decarboxylase), hydrogen peroxide generation, and, most importantly, its antioxidant characteristics **(Conney et al., 2003).**

Indeed, one of curcumin's most notable qualities is its ability to neutralize free radicals (**Sharma et al.,2005 ;Barik et al.,2005)**, especially hydroxyl and superoxide anion, resulting in a protective effect against lipid and DNA radical damage ; these modifications play a key role in carcinogenesis and atherosclerosis. Curcumin has also been proven to decrease inducible NOS activity (iNOS), an enzyme that creates nitric oxide [NO], which has a role in carcinogenesis among other things **(Chan et al.,1998).**

Curcumin's capacity to inhibit Cytochrome P450 phase I metabolism (CYP) enzymes and increase glutathione type S-transferase (GST) or epoxide hydrolase phase II enzymes is one of the other possibilities for its anticancer activities. Curcumin's preventive properties



against numerous toxic substances and mutagens are reflected in these actions **(Sharma et al.,2005 ; Dinkova-Kostova et al.,1999)**.

Figure 35: Molecular targets of curcumin in the control of death and cell Proliferation **(Duvoix et al., 2005).**

Finally, curcumin inhibits cancer cell dispersion and tumor growth by interfering with angiogenesis and cell adhesion, giving it potent antimetastatic capabilities. Curcumin has been found to decrease angiogenesis and the production of angiogenic growth factors in vivo **(Arbiser et al.,1998)**. Similarly, studies have demonstrated its effect on cell adhesion, as well as the expression of adhesion molecules such as -catenin, Ecadherine, and activated protein C (APC) and membrane surface molecules **(Gupta et al.,1999 ; Jaiswal et al.,2002)**.Curcumin also suppresses the generation of cytokines that promote tumor growth, such as TNF and interleukin-1 (Il-1) **(Chan et al.,1995)**.

Ⅱ.4 Curcumin has an antioxidant effect on the kidneys:

Curcumin has also been found in recent studies to reduce the occurrence of multiple resistance, commonly known as multi-drug resistance (MDR), which is one of the most common causes of chemotherapy failure in cancer patients. This is due to a reduction in anticancer compound cellular efflux due to transport inhibition by MRP1 (multidrug resistance protein 1) or P-gp (P-glycoprotein) **(Chearwae et al.,2005 ;Tang et al.,2005).**

Curcumin causes apoptosis in cancer cells by activating caspase pathways or increasing cytochrome C production, as well as blocking apoptotic inhibitory pathways such Bcl-2, Bcl-XL, and the IAP protein. It also inhibits proliferation and cell survival pathways like MAPKinases [JNK, ERK], JAK/STAT, AkT, and kinase C. ERK stands for extracellular signal-regulated kinase, JNK stands for c-Jun N-terminal kinase, Jak stands for Janus kinase-signal transducer and activator, and PKC stands for protein kinase C **(BERNARD et al., 2005)**.

Curcumin's renoprotective effects have been linked to three main factors : first, reducing oxidative stress by (a) preventing O2 production and scavenging different reactive oxygen species, and (b) preventing Nrf2 degradation via the ubiquitin proteosoma pathway, resulting in an increase in many antioxidant enzymes. Curcumin has also been proven to lessen inflammation by inhibiting inflammatory transcription factors like NF-B and TNF-. Reduced levels of cytokines like TGF- or CTGF, on the other hand, eventually prevent fibrosis **(Joyce et al.,2013).**

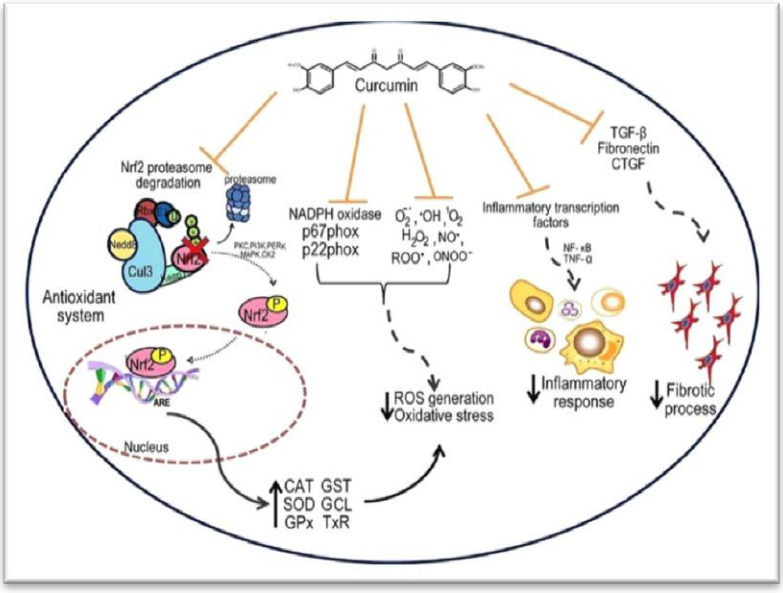


Figure 36: Curcumin has the ability to prevent kidney damage through a variety of methods **(Joyce et al., 2013).**

Curcumin therapy reduced metal-induced renal impairment, oxidative stress, and a decrease in antioxidant enzymes. Curcumin protects against hexavalent chromium (Cr VI)-induced nephrotoxicity, and this characteristic was linked to nuclear translocation of Nrf2, avoidance of oxidative stress, and preservation of antioxidant enzyme activity and mitochondrial function in the kidney. In this study, a 10-day curcumin pretreatment reduced kidney structural and functional damage, which was linked to the prevention of mitochondrial oxidant stress and a decrease in the following mitochondrial measurements : oxygen consumption (state 3), respiratory control, ATP content, calcium retention, and membrane potential. Curcumin also prevented a drop in the following: Aconitase, antioxidant enzymes, and other enzymatic activities **(Molina-Jijón et al.,2011).**

This was the first time that the preservation of mitochondrial activity was linked to the prevention of renal damage. Curcumin inhibits lipid peroxidation and reduces the following mitochondrial parameters: oxygen consumption, complex I, II, II-III, and V activity, aconitase and antioxidant enzyme activity, GSH content, membrane potential, calcium retention, and ATP content **(Molina-Jijón et al.,2011).**

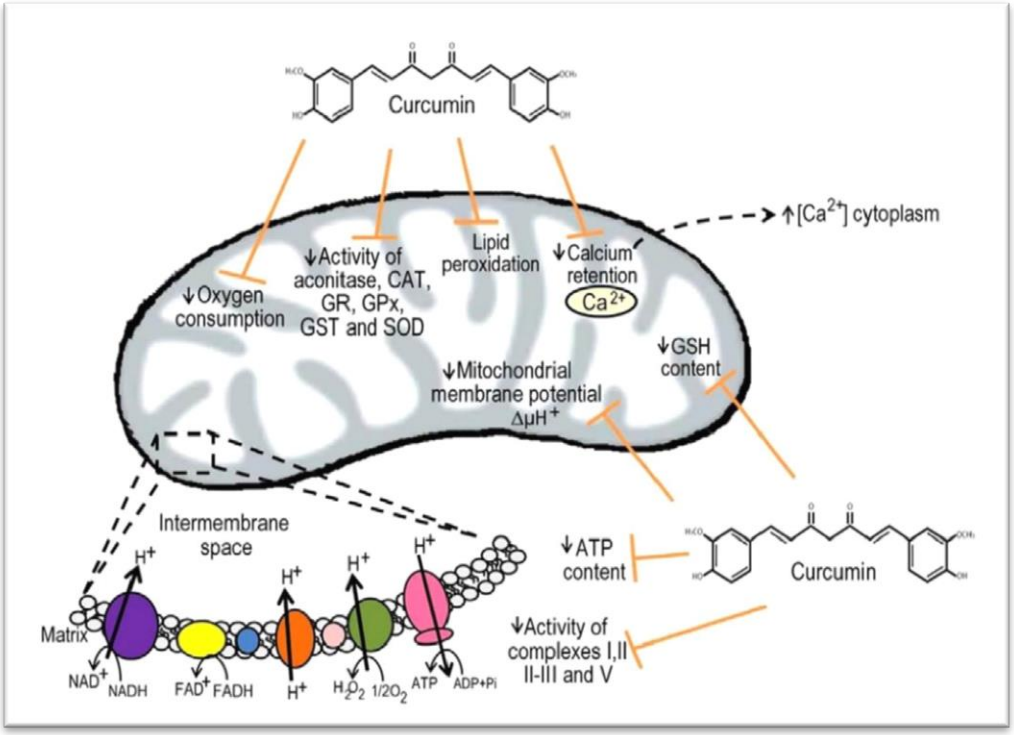
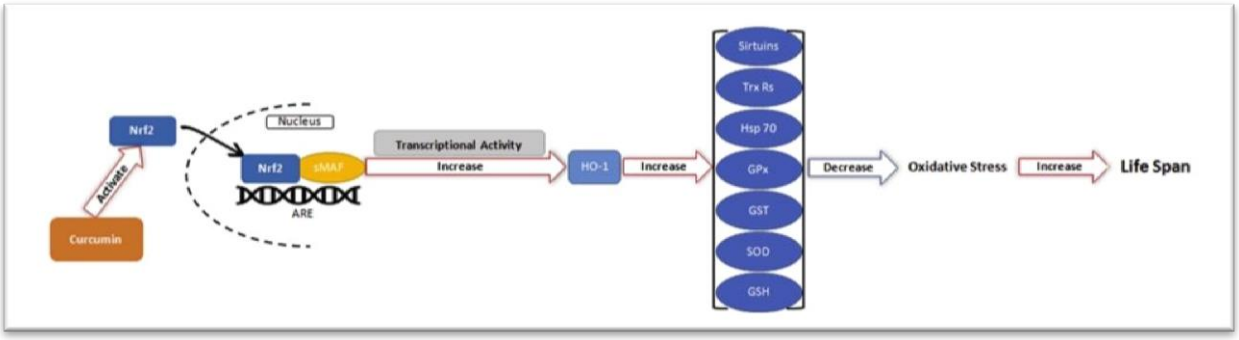


Figure 37: Curcumin can help prevent mitochondrial dysfunction in those who have had a kidney transplant **(Molina-Jijón et al.,2011).**

Ⅱ.5 Curcumin has an antioxidant effect :

Curcumin has antioxidant properties and acts as a biochemical antioxidant, as well as improving cellular antioxidant defenses. Curcumin's antioxidant activity was found to be around ten times that of vitamin E. Curcumin is a powerful antioxidant with the ability to prevent age-related cellular damage caused by reactive oxygen species production. Curcumin has a strong hydrogen-donating antioxidant action due to the presence of phenolic groups in its chemical composition.Curcumin reduces rat liver microsomal lipid peroxidation in another study, as well as in rat brain homogenates, where curcuminoids showed more effective antioxidant action than vitamin E. Tetrahydro curcumin is one of curcumin's principal metabolites, and it has been shown to remove ROS produced by hyperglycemia and increase GSH levels in cultured rat lenses.Curcumin's actions on several target molecules, both indirectly and directly linked to various metabolic functions, have been characterized, and certain clinical trials with curcumin in patients have demonstrated these potent effects. In flies that were pretreated with curcumin and then exposed to H2O2, a significant increase in the proportion of survivors was seen. Curcumin's effect on longevity in D. melanogaster was investigated, and its relationship with Curcumin-mediated SOD activities was clarified. They

discovered that increasing the amount of curcumin in the meal resulted in increased SOD



activity in both male and female Drosophila **(Aliabbas Zia et al.,2021).**

Figure 38: The effect of curcumin on the oxidative stress pathway and lifespan.The Nrf2/HO-1 signaling pathway is activated by curcumin. It activates Hsp70, thioredoxin reductase (Trx Rs) sirtuins, and antioxidant enzymes, inhibiting oxidative damage and lengthening life span. **(Aliabbas Zia et al.,2021).**

conclusion

Conclusion:

The present manuscript is a part of the Biotechnologic valorization of local and traditional natural products, Opuntia ficus-indica (OFI) and Turmeric, known by its beneficial properties but not exploited enough, this work aims to formulate different recepies in gummy form with quality controle and stability test as dietary supplements based on natural products, and indicated for the improvement of digestive disorders and general health and well being.

- An ancestral technic of extraction as Cold Enfleurage was used to prepare the plant extract in order to concerve thermo sensitive secondery metabolits and improuve their solubility, biovailibility and reactive form.
- Different reciepies with an optimal non-toxic dose of plant crud or pulp were tested in verying forms: added or free of sugar and preservatives, in order to test organoleptic proprieties, and stabilty.
- All obtained forms were tested according to national standards, which gave satisfactory results and are suitable to be produced and commercialized in local market, which dosn't need sanitary insurance according to the CNPM.
- Obtained results gave good quality controle: Microbiological and physico-chemical, for all tested formulation and a good stability in time under 20°C, besides as a deduction the formulations don't need an addition of preservatives or sugar, it can be proposed naturaly.
- Finaly insillico investigations on their structure activity relation SAR and synergetic effect between secondery metabolits were conducted in order to understand and establish how they work together in crud for guiving a better therapeutic effect than majoritary compound alone and think about the way to ameliorate it by hemisynthesis inspired by natural synergetic effect model.

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Abstract

Abstract:

The present manuscript is a part of the valorization of local and traditional natural products, Opuntia ficus-indica (OFI) and Turmeric, it aims to formulate different recepies in gummy form with quality controle and stability test as dietary supplements based on natural products, and indicated for the improvement of digestive disorders and general health and well being.

An ancestral technic of extraction as Cold Enfleurage indicated to concerve thermo sensitive secondery metabolits was used to prepare the plant extract.

Different reciepies with an optimal non-toxic dose of plant crud or pulp were tested in verying forms: added or free of sugar and preservatives.

All obtained forms were tested according to national standards, and dosn't need sanitary insurance according to the CNPM.

Obtained results gave good quality controle: Microbiological and physico-chemical, for all tested formulation and a good stability in time for 15 days under 20°C, besides as a deduction the formulations don't need an addition of preservatives or sugar, it can be proposed naturaly.

Finaly insillico investigations on their structure activity relation SAR and synergetic effect between secondery metabolits were conducted in order to understand and establish how they work together in crud for guiving a better therapeutic effect than majoritary compound alone and think about the way to ameliorate it by hemisynthesis inspired by natural synergetic effect model.

Abstract:

Résumé:

Le present manuscript s'incrit dans le cadre de la valorization Biotechnologique des produits locaux et utilisés dans la cuisine traditionnelle à savoir : Opuntia ficus-indica (OFI) and le curcuma connus en medecine traditionnelle pour leurs propriétés thérapeutiques avérées.

Le travail a consisté en la formulation de differentes recettes de Gummies ainsi que leur contrôle qualité et stabilité dans le temps afin de les proposer comme suppléments diététiques naturels indiqués pour l'amélioration du tract digestif et le bien etre.

Pour ce faire, une technique ancéstrale pour l'extraction des metabolite secondaires thérmosensible à savoir l'Enfleurage à froid a été utilisée.

Differentes formules gélifiées ont été testées en utilisant une dose optimale non toxique d'extrait brut ou de pulpe, avec de variables déclinaisons : ajout de sucre et conservateurs, afin de tester leur effet sur le gout et la conservation du produit final.

Les formes obtenus ont été testées selon les norms nationales et ont donnés un résultat satisfaisant qui n'a besoin d'une autorisation sanitaire et l'accord du CNPM pour la commercialisation.

Les resultats obtenus indiquent une bonne qualité microbiologique et physico-chimique ainsi qu'une bonne stabilité dans le temps à une température inférieure à 20°C pour toutes les formules testées, cela indique que le sucre et le concervateur peuvent etre éliminés et présenter le produit final sous sa forme naturel sans ajouts.

En fin, une étude insillico sur la relation structure activité ainsi que l'effet synergetique entre les differents metabolites secondaires presents dans l'extrait brut a été presentée dans le but de comprendre et d'établir la façon dont ils travaillent ensemble pour donner un effet thérapeutique optimale meuilleur que celui du métabolite secondaire majoritaire seule, et reflichir a améliorer son effet par l'hémisynthèse en s'inspirant du modèle synergétique naturel.

Abstract:

خلاصة:

هذه المخطوطة هي جزء من تقييم التكنولوجيا الحيوية للمنتجات المحلية وتستخدم في المطبخ التقليدي، و هي: التين الشوكي والكركم، المعروفين في الطب التقليدي بخصائصها العلاجية المثبتة .

تألف العمل من صياغة وصفات العلكة المختلفة بالإضافة إلى مراقبة الجودة والاستقرار بمرور الوقت من أجل اقتراحها كمكملات غذائية طبيعية موضحة لتحسين الجهاز الهضمي والرفاهية.

للقيام بذلك، تم استخدام تقنية إضافية لاستخراج المستقلبات الثانوية العلاجية، وهي التورم البارد .تم اختبار تركيبات هلامية مختلفة باستخدام جرعة مثلى غير سامة من المستخلص الخام أو اللب، مع اختلافات مختلفة: إضافة السكر والمواد الحافظة، من أجل اختبار تأثيرها على طعم المنتج النهائي والحفاظ عليه .وقد تم اختبار الاستمارات التي تم الحصول عليها وفقا للمعايير الوطنية وأعطت نتيجة مرضية لا تتطلب ترخيصا صحيا وموافقة المجلس الوطني لتسويقها .

تشير النتائج التي تم الحصول عليها إلى جودة ميكروبيولوجية وفيزيائية كيميائية جيدة بالإضافة إلى استقرار جيد بمرور الوقت عند درجات حرارة أقل من 20 درجة مئوية لجميع الصيغ المختبرة، وهذا يشير إلى أنه يمكن التخلص من السكر والمواد الحافظة وتقديم المنتج النهائي في شكله الطبيعي دون إضافات .

وأخيرا، قدمت دراسة عن علاقة بنية النشاط وكذلك التأثير التآزري بين مختلف المستقلبات الثانوية الموجودة في المستخلص الخام من أجل فهم وتحديد كيفية عملها معا لإعطاء تأثير مطحنة علاجية مثلى من تأثير المستقلب الثانوي الأولي وحده، والانعكاس لتحسين تأثيره عن طريق عملية التمثيل المائي القائمة على النموذج التآزري الطبيعي.

Academic year : 2021-2022	**Presented by:** ABDELMOUMENE SALMA BOUDOURI SIRINE

A gummy formulation and quality control of natural dietary supplements for the improvement of digestive disorders, general health and Well being.

Thesis for the Master's degree in Biochemistry

The present manuscript is a part of the valorization of local and traditional natural products, Opuntia ficus-indica (OFI) and Turmeric, it aims to formulate different recepies in gummy form with quality controle and stability test as dietary supplements based on natural products, and indicated for the improvement of digestive disorders and general health and well being.

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keywords: Opuntia ficus-indica (OFI) , curcuma , gummy, digestive, dietary supplements.

research laboratories:

Laboratoire of

Supervisor : Mme MOUAS T NERDJAS (Prof - Mentouri Brothers University, Constantine 1).

Examiner 1 : Pr.DJEDOUANI AMEL (ENS Constantine3)

Examiner 2 : Dr.TABBI AOUATEF (ENS Constantine3)