Investigation in to Herbal Colorectal Cancer Treatments

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Abstract:

This study is a descriptive and analytical approach to medicinal plants used in phytotherapy for colorectal cancer (CRC), through a bibliographic research followed by an online ethnobotanical survey, targeting patients, their relatives, and herbalists, mainly from the Setifprovince. In order to know the curative and preventive effects of the identified plants. The survey targeted 50 participants, of which 92% are from Setif, Algeria, 71.43% are men and 28.57% are women, 27.77% are aged between 20 and 50 years, and 73.47% are aged over 50 years. This questionnaire revealed that 12 species of plants are identified. All these species have already been researched by researchers and proven their therapeutic virtues. These plants are considered effective in treating colorectal cancer, with garlic (*Allium sativum*) being the most frequently mentioned species with a percentage of 27.27%. In light of the results of this survey, 98% of patients resort to traditional medicine through the use of a single plant, while 02% use a mixture of plants. It also appears that patients are familiar with medicinal plants, their benefits, and their uses in treating CRC.

Key words: Colorectal cancer, survey, phytotherapy, medicinal plants.

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Introduction

Colorectal cancer (CRC) is a malignant tumour that develops from the cells that line the inner lining of the colon or rectum. It is caused by mutations in the genes that cause errors in DNA replication. These mutations transform the initially normal cells into cancerous cells in an anarchic fashion, until they form a malignant tumour. Most often, these malignant tumours originate from a benign tumour, called an adenomatous polyp, which evolves slowly and eventually becomes cancerous (Meddah*et al.*, 2009).

Colorectal cancer is the third most common cancer worldwide, in both sexes, and more frequently in men than women. In men, CRC is the third most common cancer after prostate and lung tumours, accounting for 14% of total cancer incidence. In women, CRC accounts for 13% of new cancer cases and is the second most common tumour after breast cancer. In terms of incidence, it affects the colon in 60% of cases and the rectum in 40%. CRC varies from country to country according to the human development index.Although the incidence of CRC varies considerably from one region of the world to another. CRC accounts for more than 9% of total cancer incidence, with more than 1.8 million new cases. However, in terms of mortality, it ranks second, with nearly 881,000 deaths/year, representing approximately 10.2% of all cancer-related deaths in 2018 (Marley *et al.*, 2016; Favoriti*et al.*, 2016).

In Algeria, colorectal cancer, with 150 new cases per year, is one of the most common cancers in the country. It accounts for 55% of digestive cancers, despite the therapeutic developments that have emerged (Negrichi*et al.*, 2017).

Colorectal cancer is a cancer whose incidence increases with age. In both sexes, 94% of colorectal cancers occur in people over the age of 50. The average age of onset of colorectal cancer is 71 in men and 75 in women (Manceau*et al.*, 2014). It is associated with a low-fibre diet and high consumption of red meat (particularly beef), processed meat (salted, smoked, etc.) and cooked meats. A high-calorie, high-fat diet increases the risk of colorectal cancer (Scotte*et al.*, 2002).

Alcohol consumption and smoking increase the risk of colorectal cancer in men, particularly rectal cancer. The risk is higher in heavy smokers and long-term smokers (Mizukami *et al.*, 2017).

Colorectal cancers linked to a precisely identified genetic mutation account for 5% of cases. There are two forms: familial adenomatous polyposis and hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome. In the majority of cases, the genes involved are members of the MMR or Mis Match Repair family (MSH2, MLH1, MSH6). People with a mutation in one of these genes have a 40-70% risk of developing colorectal cancer before the age of 70 (Steinke *et al.*, 2013).

Chronic inflammatory bowel disease (IBD), such as Crohn's disease and ulcerative colitis, increases the risk of cancer, particularly when it has been present for more than 10 years.Several approaches can be used to treat colorectal cancer, including surgery (Libuttie*t al*., 2018), radiotherapy for cancers of the rectum, chemotherapy(Gill *et al.,* 2003), targeted therapies and immunotherapy (Bokemeyer et *al*., 2015). The choice of colorectal cancer treatment depends on the stage and location of the cancer and the patient's general condition. Although these standard treatments have undergone significant advances in recent years, they can have major side-effects that limit their use in some patients and can reduce patients' quality of life. As a result, there is growing interest in the use of phytotherapy, an alternative practice that involves using medicinal plants to treat a range of conditions, including colorectal cancer. Although herbal medicine is not yet widely accepted in the medical field, there is growing evidence that certain plants may have benefits for colorectal cancer patients, due to their anti-inflammatory, antioxidant and anti-tumour capabilities.In this context, this work is being carried out to prepare scientific support on phytotherapy for colorectal cancer.

Phytotherapy for colorectal cancer

Medicinal plant-based drugs for the treatment of colorectal cancer are one of the complementary approaches with few side effects. At the beginning of using this type of treatment, it is necessary to determine the stage and severity of the disease. There are several plants already used in the case of colorectal cancer for curative or preventive purposes:

Camellia sinensis

- **Botanical description and origin**

*Camellia sinensis or Thea sinensis (*Theaceae or Tea plant), commonly known as Tea, is native to Asia and is a shrub belonging to the *Theaceae* family. It is characterized by dark green, persistent, fragrant, axillary, and solitary leaves, very branched, reaching 10 dm to 15 dm, up to 20 dm for certain varieties. Their size varies and can reach up to 03 cm (Fig. 01). The pointed young buds and leaves that will produce tea are harvested. The tea plant requires a warm and humid climate and can be cultivated up to 3000 m altitude. Harvesting begins in spring (early April) and continues until autumn (Arnal-Schnebelene*t al*., 2008; Debuiguee*t al*., 2009).

Fig. 01: Appearance of the *Camellia sinensis* plant.

➢ Active compounds

The main active ingredients of green tea include polyphenolic compounds such as epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG) (Fig. 02), all of which may be responsible for the anti-carcinogenic and anti-mutagenic effects of green tea. Other polyphenols include flavanols and their glycosides and depsides such as chlorogenic acid, quinic acids, carotenoids, trigalloylglucose, lignin, proteins, chlorophyll, minerals (aluminum or manganese, depending on soil content), caffeine, and a very small amount of methyl xanthines (Steinmann *et al*., 2013; Cardoso *et al*., 2022).

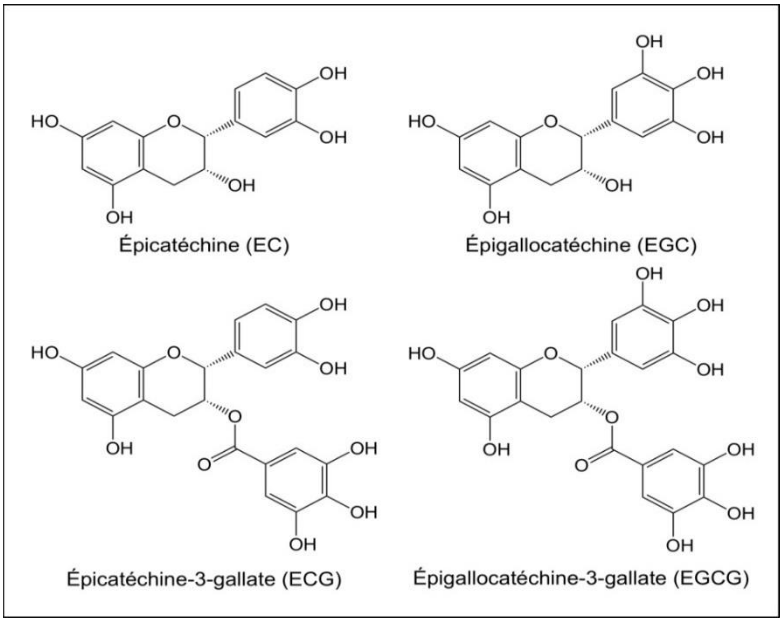


Fig. 02: Main active ingredients of *Camellia sinensis*.

➢ Mechanisms of action

Green tea primarily exerts its anticancer effect, in the case of CRC, through its major active ingredient, EGCG, which has a pro-apoptotic and anti-proliferative effect through:

- Induction of apoptosis and inhibition of the cell cycle in many cancer cells such as HCT-116 colon cancer cells, while having no effect on normal cells (Ahmad *et al*., 1999).
- Induction of apoptosis in cancer cells by stimulating nuclear condensation through activation of caspase-3 and cleavage of poly (ADP-ribose) polymerase (Gosslau*et al*., 2011).
- Activation of mitochondrial membrane depolarization and release of cytochrome c into the cytosol (Lambert *et al*., 2010).
- Ability to directly block cyclin-dependent kinases, which is the main event in cell cycle progression (Lawless *et al*., 2010).
- Decrease in cyclin D1 expression and increase in retinoblastoma phosphorylation (Liu *et al*., 2017).
- Inhibition of epidermal growth factor receptor (EGFR) activation, human epidermal growth factor receptor 2 (HER2) (Ahmad *et al*., 1999; Khan *et al*., 2013).
- Suppression of nuclear factor kappa-B (NF-kB), which is the essential sensitive element of oxidative stress transcription factors (Khan *et al*., 2013; Gupta *et al*., 2014). Inflammation, cell proliferation, and cancer cell death are just a few of the biological responses regulated by NF-kB transcription, which plays an essential role in this process.
- Stimulation of endothelial nitric oxide synthase and inhibition of mitogen-activated protein kinases (MAPK), such as ERK, JNK, and p38.
- Inhibition of tumor necrosis factor (TNF-α) action, which in turn triggers the apoptosis process (Han *et al*., 2022).

The polyphenols produced from green tea exert their anticancer effects through modifications of histones, microRNAs, and DNA methylation (Bag *et al*., 2018). Similarly, catechols regulate both the G1/S and G2/M transitions and also prevent proliferation and DNA synthesis (Liu *et al*., 2017).

Allium sativum L.

- **Botanical description and origin**

Garlic or Allium sativum is a bulbous, perennial, monocotyledonous plant belonging to the Liliaceae family. This plant is native to Central Asia and has gradually spread to the Far East, Egypt, and the Mediterranean Basin. It is transported by merchants along trade routes (Geaga, 2015), but it has recently been cultivated in many regions of the world, including Europe, North Africa, Asia, North America, and West Africa (Gambogou*et al*., 2019).

Garlic is characterized by a bulb with a strong odor and taste, consisting of cloves (garlic bulbs, bulbils) that do not exceed fifty centimeters in height. The white or pink flowers in umbels are enclosed before flowering in a membranous spathe with a very long tip (Callery, 1998). The leaves are long, flat, and smooth with a cylindrical, hollow, linear, flat, and pointed tip leaf blade (Fig. 03) (Gambogou*et al*., 2019). Garlic adapts to all climates, but it yields the best crops in temperate countries (Cavagnaro*et al*., 2007). Generally, the most used part of garlic in phytotherapy is the bulb.

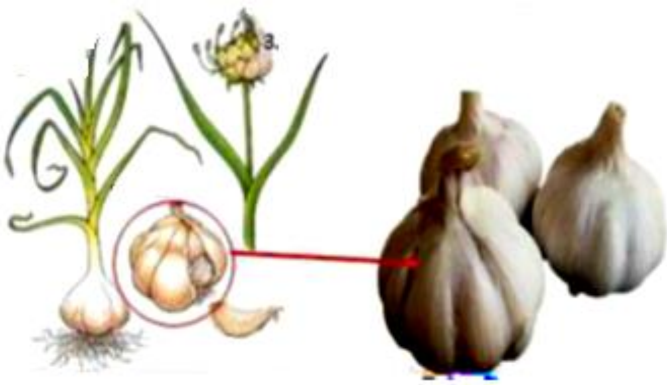


Fig. 03:Presentation of Garlic

- **Active compounds**

Numerous studies show that organosulfur compounds in garlic play an important role in the prevention of certain cancers such as CRC. The main compounds present in the garlic bulb are: allicin, diallyl sulfide (DAS), diallyl disulfide (DSDA), diallyltrisulfide, diallyltetrasulfide (TSDA), allylmethyl sulfide, S-allylmercapto-cysteine (SAMC), Z-ajoene, thiacreone, and methyl-L-selenocysteine (Fig. 04) (Oravetz*et al*., 2023).

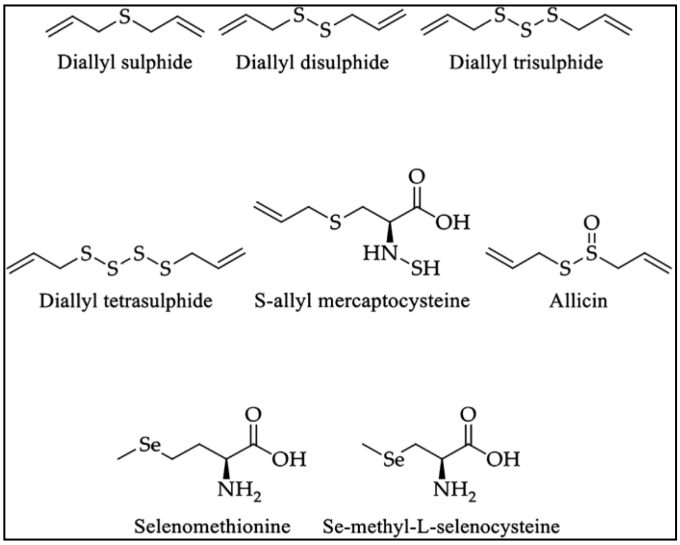


Fig. 04: Some molecular structures of organosulfur compounds in garlic.

➢ **Mechanisms of action**

Several mechanisms of action have been proposed for CRC therapy, but the precise mode of action is still unknown. By modifying cytokinesis and preventing NF-kB activity in neighboring tissues through proteasomal degradation of TRAF6 in effusion lymphoma (Shigemi*et al.*, 2016). The proliferation of malignant cells is interrupted during the cell cycle by organosulfur compounds (Singh *et al.*, 2018). Similarly, in 2023, Oravetz and colleagues showed that garlic extracts and its individual constituents had cytotoxic, cytostatic, antiangiogenic, and antimetastatic activities in different in vitro and in vivo models of colorectal cancer. The molecular mechanisms of their antitumor effects are also associated with the modulation of several well-known signaling pathways involved in cell cycle progression, particularly the G1-S and G2-M transitions, as well as intrinsic and extrinsic apoptotic pathways as follows (Fig. 05) (Oravetz*et al.*, 2023):

➢ SAMC (S-allyl-mercaptocysteine): blocks the cell growth of metastatic CRC cells by activating the TGF pathway (Tong *et al.*, 2014). It disrupts cellular microtubules that form the cytoskeleton and mitotic spindle in cancer cells. As a result, cell divisions are interrupted. It also induces apoptosis by activating caspases (Omar *et al.*, 2010).

➢ DAS: inhibits the MAPK/ERK pathway (Sriram*et al.*, 2008). This is due to the increase in Glutathione-S-transferase concentration, an enzyme involved in the detoxification of carcinogens. It also acts on cytochromes P450, a family of enzymes involved in the activation of carcinogenic elements.

- DADS: inhibits cell viability by inducing cell cycle arrest in the G2/M phase followed by apoptosis through caspase-3 cleavage and alteration of the Bcl-2/Bax ratio and inhibition of the MAPK/ERK pathway-activated protein kinase (Yin *et al.*, 2014).
- TSDA: inhibits tubulin polymerization via oxidation of cysteine residues C12 and C354, leading to mitotic arrest. It induces cell line arrest of CRC by reducing CDK1, Cdc25B, and C, resulting in CDK1 inactivation through phosphorylation of its Tyr 15 residue. Exposure to TSDA also leads to the accumulation of cyclin B1 and securin, which control the metaphase/anaphase transition. Finally, DNA fragmentation and apoptotic body formation occurred in both cell lines (Xiao *et al.*, 2009).

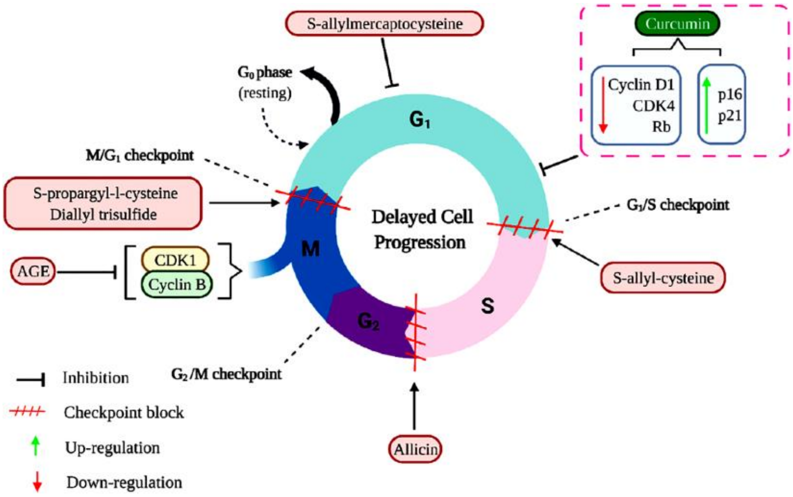


Fig. 05: Mechanism of action of organosulfur compounds in garlic and active molecule of turmeric.

Zingiber officinale

- **Botanical description and origin**

*Zingiberofficinale*or ginger, is a well-known medicinal plant, belonging to the Zingiber genus and the Zingiberaceae family. It is a perennial, aromatic, and monocotyledonous herbaceous plant. It is cultivated in tropical and sunny areas, mainly in Asia, India, China, and Nepal *(*Baraga *et al., 2006).*

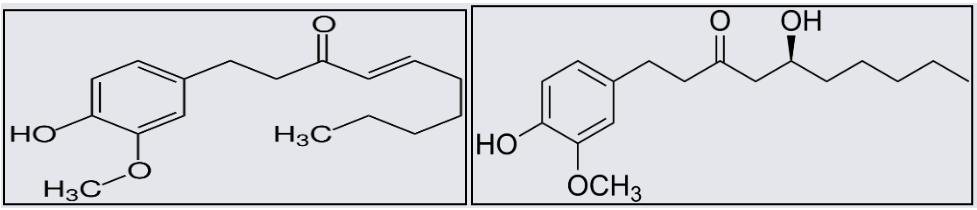
- An underground part: called the rhizome, which is knotty and branched.
- An aerial part: formed by leaves and a stem about one meter tall.

The pulp of the rhizome is yellow on the inside, and the leaves are alternate, lanceolate, and fragrant. The flowers are yellow with a red lip. The ginger fruits contain few black seeds. It multiplies and reproduces mainly through the division of its rhizome (Fig. 06) (Fiavre*et al*., 2006).

Fig. 06: Appearance of the ginger plant.

➢ Active compounds

The ginger rhizome is used for the treatment of colorectal cancer (CCR). It contains oleoresin composed of shogaol and gingerol (Fig. 07), which have anti-inflammatory, antiemetic effects, and accelerate intestinal transit. It also contains essential oil, numerous vitamins (B1, B2, B3, and C), and minerals (Gigon, 2012).



ShogaolGingerol

Fig. 07: Some bioactive components of ginger.

➢ Mechanisms of action

Ginger leaf extract induces apoptosis in the case of human colorectal cancer, through the activation of caspase 9, caspase 3, and transcription factor 3 (ATF3), which induce apoptosis in cancer cells by regulating the ERK1/2 pathway. Ginger also interacts with cAMP and activates ATF3 (Tang *et al*., 2002; Park *et al*., 2014). It downregulates the expression of the MMP-2 gene and the K-RAS marker. The latter is responsible for colorectal metastases by regulating VEGF, protease expression, apoptosis, adhesion, and motility (Lavrado*et al.*, 2015).

Similarly, ethanol extract and paradol, dehydrogingerdione, and gingerdione inhibit the proliferation of human colon cancer cells by arresting the cell cycle in the G0/G1 phase and decreasing DNA synthesis (Sang *et al.*, 2009).

Ginger leads to a reduction in the expression of miR-130 (micro RNA precursor) with an increase in the genetic expression of NKd2 (NaKedcuticle 2), which are tumor suppressor genes, by inhibiting the Wnt/β-catenin pathway through the decrease in protein accumulation of β-catenin, axin, and TCF4 (Transcription Factor 4).

6-gingerol and zingerone have antimitotic activity, they modulate signaling molecules and regulatory proteins of cell growth such as NF-κB, CDK, MMP-9, STAT3, MAPK, PI3K, CIAP-1, XIAP, Bcl-2, caspases, ERK1/2, Akt, TNF-α, COX-2, cyclin D1 (Fu *et al.*, 2014).

Curcuma longa

- **Botanical description and origin**

Curcuma longa or turmeric, in Algeria, is a species belonging to the Zingiberaceae family, native to South or Southeast Asia and India, hence the name saffron. It is an herbaceous, perennial plant with yellow flowers and broad leaves. It provides an underground rhizome (Fig. 08). This aromatic species grows in a tropical climate, requires a rich but well-draining soil, watering in high heat, in bright exposure, and in a warm climate (Mbadiko*et al.*, 2017).

Fig. 08: Appearance of the Curcuma longa plant.

- **Active compounds**

The rhizome is the part used in herbal medicine, in powder form. It mainly contains polyphenols, curcuminoids (Fig. 09) (curcumin, monodemethoxycurcumin, bidesmethoxycurcumin), and an essential oil rich in zingiberene (Fondu, 2020).

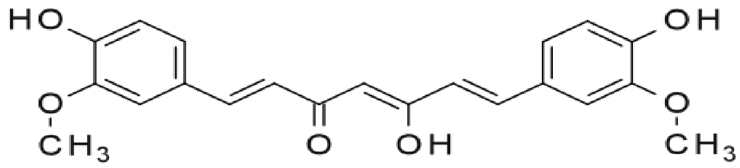


Fig. 09: Chemical structure of curcumin.

➢ **Mechanisms of action**

Curcumin is the most commonly used active ingredient in phytotherapy, used as an additive supportive treatment by increasing the response of tumor cells to chemotherapy and radiotherapy. It also exerts an anticancer effect through (Deogade andGhate, 2015):

✓ Suppression of NF-κB activation through inhibition of E2F-1 transcription factor and thymidylate synthase, resulting in cell cycle arrest at the G0/G1 phase, with a concomitant decrease in the number of cells in the S phase.

✓ Decreased levels of cyclin D1, CDK4, and pRb, and increased levels of p16 and p21 in both colorectal cancer cell lines (HCT116 and HT-29), significantly reducing tumor growth (Rajitha*et al.*, 2016).

✓ Induction of apoptosis and modulation of different signaling pathways, such as mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), p38, and Jun N-terminal kinase (JNK) (Li *et al.*, 2008; Lee *et al.*, 2019).

Rosmarinusofficinalis

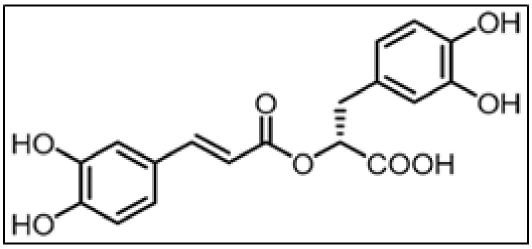
➢ **Botanical description and origin**

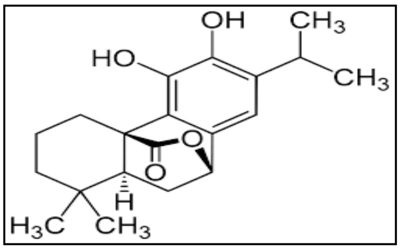
Rosmarinusofficinalis, commonly known as rosemary, is an aromatic medicinal plant that belongs to the*Lamiaceae* family and the *Rosmarinus* genus. Rosemary is naturally found in the Mediterranean basin from Portugal to Turkey, and from Morocco to Cyrenaica in the south. It is a bushy evergreen shrub, approximately 1 meter tall, with woody stems. The rosemary leaves are tough, persistent, sessile, linear, and rolled at the edges. The flowers are pale blue to whitish and practically sessile. The fruit is a dark brown, smooth, and globular tetra-achene, measuring 2 to 3 mm. Rosemary has a dense and deep root system, allowing it to draw water from deep sources (Fig. 10) (Comas *et al.,* 2013). The essential oil and leaf extract are the most commonly used preparations in phytotherapy.

Fig. 10: Appearance of *Rosmarinusofficinalis.*

➢ Active compounds

The extract of *Rosmarinusofficinalis L.* contains several molecules, such as rosmarinic acid (Fig. 11), camphor, caffeic acid, ursolic acid, betulinic acid, carnosic acid, and carnosol. Similarly, the essential oil of rosemary is mainly composed of phenolic compounds (diterpenes and triterpenes), which possess antioxidant and anticancer properties (Aumeeruddy*et al.*, 2015).





Rosmarinic acid Carnosol

Fig. 11: Chemical structure of active molecules in *Rosmarinusofficinalis.*

➢ Mechanism of action

The active components of rosemary are phenolic elements (diterpenes and triterpenes), characterized by a chemical configuration of hydroxylated aromatic cycles. Carnosic acid and carnosol block the antigenic functions of endothelial cells, such as differentiation, proliferation, and consequently tumor progression (Allegra *et al.*, 2020).

- ✓ Treatment with carnosol induces programmed cell death in HT-29 and HCT116 cancer cells by inhibiting p53 stimulation and caspase 3 and 9 cleavage through the inhibition of JAK2 and Src kinase phosphorylation.
- ✓ Carnosic acid blocks the STAT3 reporter gene activity, such as cyclins D1, D2, and D3. It also induces ROS production in colon tumor cells, amplifying their destruction (Kim *et al*., 2015).
- ✓ Rosemary extract has antiproliferative effects by inhibiting proliferative signaling pathways such as PI3K/AKT, and by modulating the Nrf transcription factor pathway (Valdé*et al*., 2016).

Furthermore, in vivo studies have revealed that treatment with a mixture of rosemary and turmeric inhibits tumor growth in mice transplanted with CT-26 cells, without any side effects such as weight loss or changes in renal and hepatic functions. Similarly, mice treated with this mixture showed a significant increase in the cytotoxic T lymphocyte (CTL)/Treg cell ratio. These results have shown that the combination of rosemary and turmeric can inhibit the growth of cancer cells in the CT-26 cell line and reduce tumor growth in colorectal cancer mice (Makarema*et al*., 2020).

Salviaofficinalis

- ➢ **Botanical description and origin**

The genus Salvia belongs to the *Lamiaceae* family. This genus is commonly called sage (Lu and Foo, 2002). It consists of more than 900 species. Salvia officinalis, or common sage, is a perennial plant native to Mediterranean regions. It is a highly branched plant with square-shaped, woody-based stems. The petiolate leaves are pale green, velvety, and oblong. The flowers, on erect floral spikes, are grouped in small clusters (Jedidi*et al*., 2018).

The sage root is brownish and fibrous. The stem measures 20 to 30 centimeters and is highly branched. The leaves are opposite, elliptical, with petioles, rough, serrated edges, reticulated, soft, whitish on the upper side, and persist throughout winter thanks to the woolly hair covering that protects them. The flowers, blue-pink lilac, visible from May to August, are large and grouped at the base of the upper leaves, forming large spikes. Common in Europe, especially in southern regions, it is rare in the wild. It reaches a height of about one meter (Fig. 12) (Jedidi*et al*., 2018).

Fig. 12: Appearance of the plant *Salvia officinalis L.*

- **Active compounds**

Salvia officinalis and *Salvia fruticosa* are Mediterranean medicinal and aromatic plants that contain rosmarinic acid (Fig. 13) as the main phenolic compound. This phenolic compound possesses antioxidant, anti-inflammatory, and anticancer properties (Xavier *et al.*, 2009).

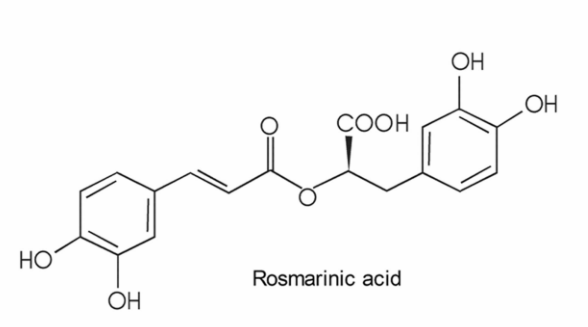


Fig. 13: Chemical structure of the active compound of *Salvia officinalis*.

- **Mechanisms of action**

According to Xavier and colleagues (2009), rosmarinic acid exerts an antiproliferative and pro-apoptotic effect on two colorectal cancer cell lines, HCT15 and CO115, through effects on the MAPK/ERK and PI3K/Akt pathways and caspase-mediated apoptosis. These two cell lines have different activating mutations in these two pathways: HCT15 has a KRAS (G13D) mutation while CO115 has a BRAF (V599E) mutation. Considering these genetic differences, we speculate on the mechanisms behind the antiproliferative and pro-apoptotic effects of sage extracts and rosmarinic acid and the involvement of PI3K/Akt. The involvement of the PI3K/Akt and MAPK/ERK signaling pathways in these effects (Fig. 14).

Rosmarinic acid inhibits ERK pathway phosphorylation in HCT15 cells but not in CO115 cells, and also inhibits mutant KRAS gene, resulting in decreased phospho levels in HCT15 cells but not in CO115 cells. On the other hand, RA does not alter ERK phosphorylation levels due to an activating BRAF mutation downstream of the RAS oncogene (Fig. 14) (Xavier *et al.*, 2009).

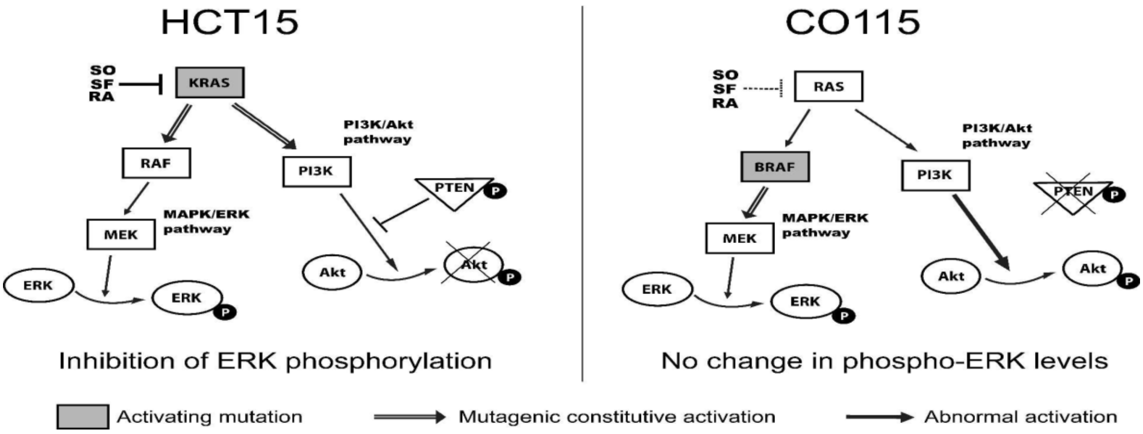


Fig. 14: Model for the inhibition of ERK phosphorylation by Salvia fruticosa (SF), *Salvia officinalis* (SO), and rosmarinic acid (RA) in HCT15 cells but not in CO115 cells.

Ephedraalata

- ***Botanical description and origin.***

Ephedra is a genus of non-flowering seed plants belonging to the family Ephedraceae, which includes about 67 species. Ephedra alata, known as andla in Arabic (Fig. 15), is the most commonly used species, mainly in desert areas of Asia, America, Europe, and North Africa (AL-Saraireh*et al.*, 2021). In Algeria, Ephedra alata is found in the northern and western Sahara in sandy terrains, regs, and sandy riverbeds.

This species is known for its high tolerance to water deficiency in Saharan regions. It is a shrub that grows 1 to 3 meters tall, with jointed and highly branched branches of a greenish-yellow color. It has small opposite leaves at the nodes, alternating from one node to another. The flowers are small whitish cones and the fruits are surrounded by widely membranous bracts (Hadjadj*et al.*, 2020). The commonly used parts in phytotherapy are the aerial parts or green stems and the fruits.

Fig. 15: Appearance of *Ephedra alata* plant

- **Active compounds**

*Ephedra alata*is a species that constitutes a natural source of several molecules, including alkaloids, tannins, phenolic acids, and flavonoids such as quercetin (Fig. 16), which exerts a powerful anticancer effect (Hegazi and Lamey, 2011).

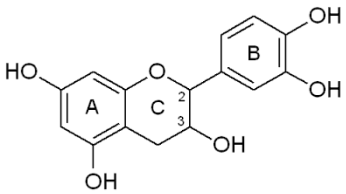


Fig. 16: Molecular structure of quercitrin from *Ephedra Alata.*

- **Mechanisms of action**

Several recent studies have revealed that E. alata could have significant anticancer potential in vivo and in vitro (Sioud*et al.*, 2022). Several mechanisms have been proposed to understand these anticancer effects, such as cytotoxicity, apoptosis, mitochondrial suppression, cell cycle arrest, inhibition of vital enzymes, reduction of DNA damage, and/or prevention of angiogenesis. Flavonoids are inhibitors of certain DNA oxidation reactions. They mainly inhibit the production of 8-hydroxydeoxyguanosine (8-OHD), a marker of oxidative DNA damage (Azadeh*et al.*, 2022).

Survey on CRC phytotherapy

Material and Methods

Study type

Based on the data collected on colorectal cancer phytotherapy mentioned in the previous chapter, an ethnobotanical survey is conducted on the frequency and mode of use of medicinal plants by patients with CRC in Algeria, particularly in the province of Setif.

Study period and location

This study lasted for one month (May - June 2023). The survey is conducted using an online questionnaire and through herbalists, mainly targeting patients from the province of Setif and their relatives, and then those from other provinces of Algeria. It is sent anonymously, allowing participants to respond with honesty and confidentiality.

Modality and conduct of the study

Data collection

The data were collected using an online questionnaire shared with patients and their relatives, as well as with certain herbalists. It is written in two languages, Arabic and French (Annex I). The questionnaire consists of questions about the informant's information, patients, and the traditional use of medicinal plants for the treatment of colorectal cancer.

1. The informant (Gender, age, level of education, and patient's relationship).
2. The patient (Age, gender, stage and type of colorectal cancer, applied treatment, etc.).
3. The medicinal plants used (vernacular names, parts used, preparation method, period of use, patient's opinion, etc.).

Participation in the study is anonymous and unique, each patient agrees to answer the questionnaire individually only once.

Statistical analysis of the data

The data were entered, expressed as percentages, and then processed and statistically analyzed using Graph Pad Prism software, version 7.00, and Excel 2016 software.III.2. Results and Discussion

The study involved 55 patients with colorectal cancer or informants. Among the 55 respondents, only 50 responses were considered, as the remaining 5 respondents were unable to identify the name of the medicinal plant used. The results are presented as follows:

Informant data

Region

The results of this survey show that the informants from the Setif Province are predominant, accounting for 92% of the 50 respondents. Informants from outside the Sétif Province represent only 8% (Fig. 17).

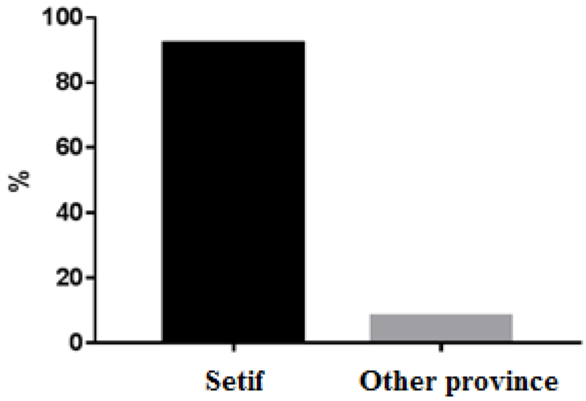


Fig. 17: Distribution of informants according to geographical region.

Gender

Among the 50 respondents in this study, 26 informants are male, accounting for 52%. On the other hand, 24 informants are female, accounting for 48% of the surveyed population (Fig. 18).

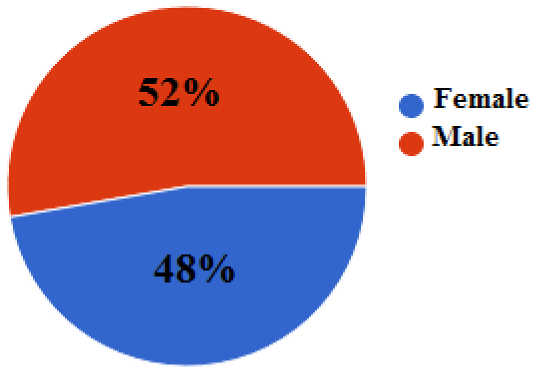


Fig. 18: Distribution of informants by gender.

Level of education

The informants in this survey have varied levels of education. The results obtained show that the most common level is master's degree, accounting for 38% (19 individuals), followed by bachelor's degree at 22% (11 individuals), followed by no high school diploma at 20% (10 individuals), and doctorate degree at 12% (6 individuals), and finally, a bachelor's degree at 8% (4 individuals) (Fig. 19).

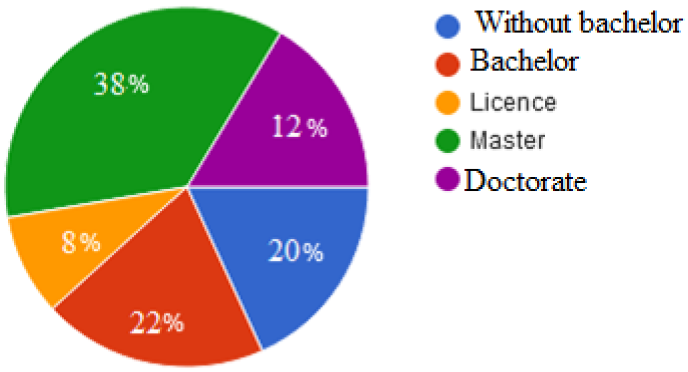


Fig. 19: Distribution of informants by level of education.

Patient data

Gender

According to the results of this survey, both men and women with colorectal cancer have resorted to phytotherapy and use medicinal plants as a traditional remedy. The prevalence of colorectal cancer is 71.43% in men and 28.57% in women (Fig. 20).

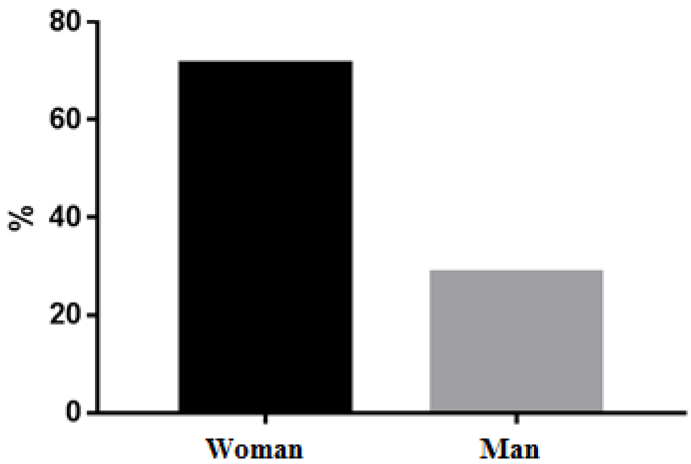


Fig. 20: Distribution of patients with colorectal cancer by gender.

Age

The results of this survey show that among the 50 patients studied, 73.47% of patients are over 50 years old, with women accounting for 27.77% and men accounting for 72.23%. Furthermore, 26.53% of patients are between 20 and 50 years old, with 23.07% being women and 76.92% being men (Fig. 21 and 22).

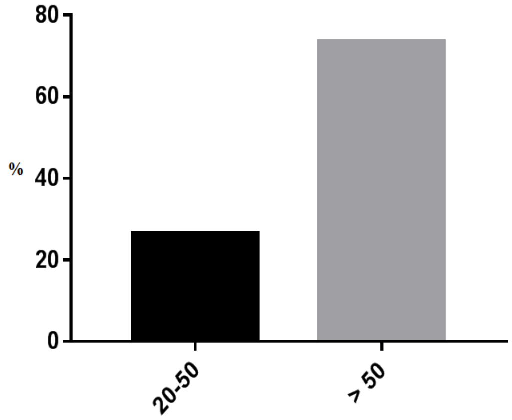


Fig. 21: Distribution of patients by age. Fig.22: Distribution of patients by age and gender.

Geographic region

According to the results of this study, patients from the Sétif Province are predominant, accounting for approximately 92% of all respondents (46/50), while only 8% of responses are collected from respondents from other provinces (Tlemcen, M'Sila, Guelma, Constantine, and Oran) (Fig. 23).

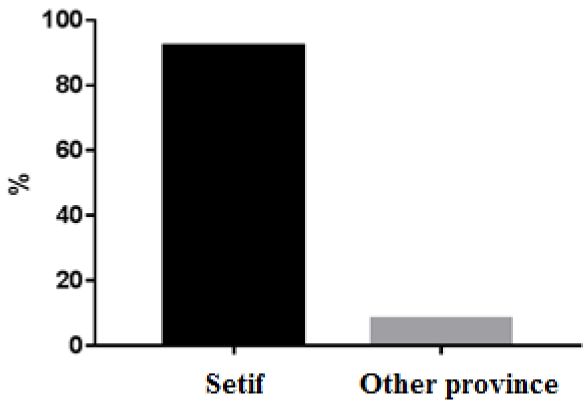


Fig. 23: Frequency of CRC according to geographical region.

Data on medicinal plants used

The survey results show that CRC patients use medicinal plants as an alternative/additive treatment in conjunction with chemotherapy and surgery. The traditional treatment of CRC with medicinal plants in the Sétif province is transmitted through herbalists and used orally by all respondents.

CRC patients who practice phytotherapy and use a single plant are 48 out of the 50 surveyed individuals who identified the plant used, representing approximately 96% of all patients. It should be noted that 10 out of the 50 surveyed individuals use more than one plant independently. However, those who use a plant mixture represent only 4%, which is 2 out of the 50 surveyed individuals (Fig. 24).

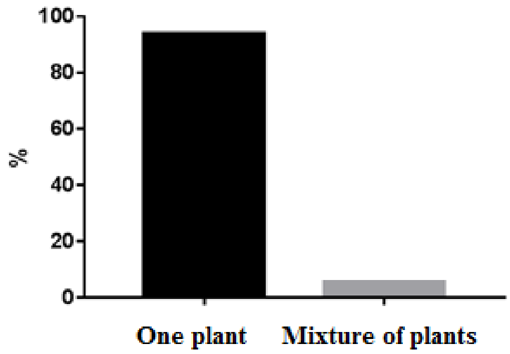


Fig. 24: Frequency of using a medicinal plant or a mixture of plants.

Condition of the used plants

The survey showed that approximately 53.70% of the plants used in CRC phytotherapy by patients are fresh, while 46.30% are dried (Fig. 25).

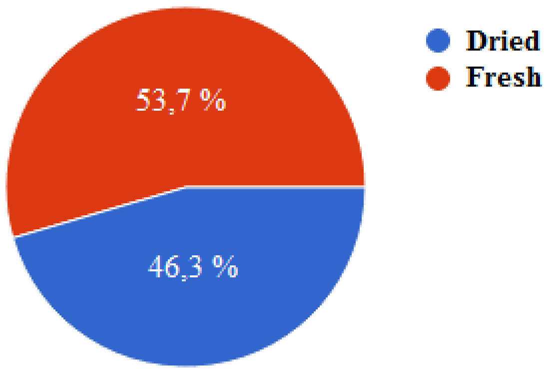


Fig. 25: Frequency of fresh and dried plant condition.

Used part

The surveyed population uses different parts of the plant. The whole plant is the most commonly used part, with a percentage of 46.30%, followed by roots at 24.07%, leaves at 11.11%, and finally seeds and stems at 9.26% (Fig.26).

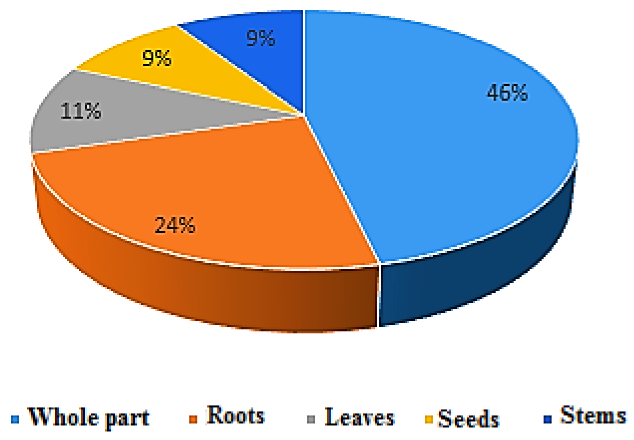


Fig. 26: Frequency of using plant parts.

Association of phytotherapy with other treatments

According to the results of this survey, 70% (35 individuals) of CRC patients were under the influence of another treatment during herbal treatment, with 51.43% of them using medication, followed by chemotherapy at 45.71%, and 2.86% undergoing surgery. Meanwhile, 30% (15 individuals) were not under the influence of any treatment during herbal treatment (Fig. 27).

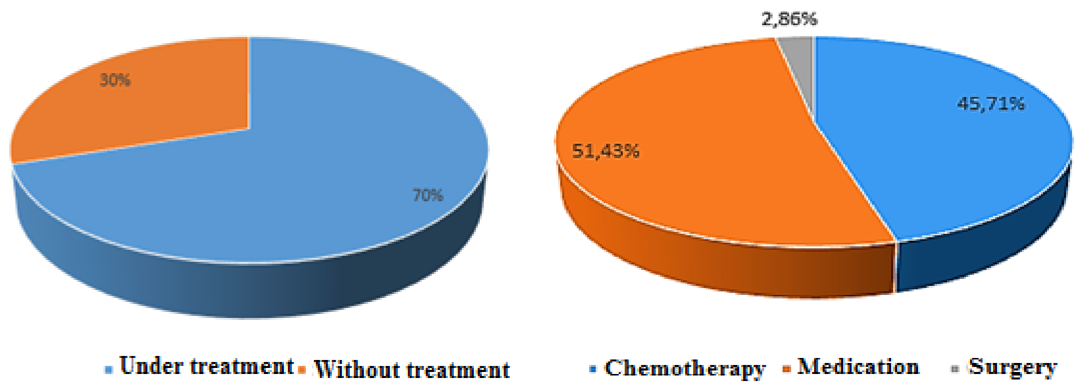


Fig. 27: Frequency of using medicinal plants in association with other treatments.

Nature of identified plants

In this survey, 12 species of medicinal plants were identified and recognized by all respondents. These plants are as follows: Garlic (*Allium sativum*), Turmeric (*Curcuma longa*), Ginger (*Zingiberofficinale*), Sage (Salvia officinalis), Andla (Ephedra alata), Green tea (Camellia sinensis), Oud ghriss (*Aquilariamalaccensis*), Fennel seed (*Foeniculumvulgare*), Licorice (*Glycyrrhizaglabra*), Pristim (Medicago sativa), Flaxseed (*Linumusitatissimum*), and Graviola (*Annona muricata*). These plants are used at varying frequencies, with garlic being the most commonly used plant (Fig. 28).

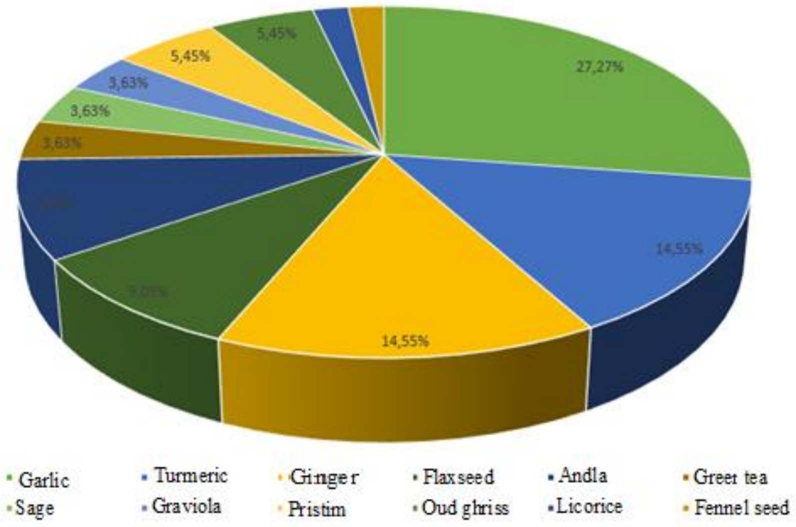


Fig. 28: Frequency of citation for each medicinal plant by CRC patients.

- ***Allium Sativum***

The results of this survey show that the most commonly used species by CRC patients is Garlic (Allium sativum), with a citation frequency of 27.27%, among all the plants used by CRC patients, accounting for 15 out of the 50 surveyed patients. This plant is used as a curative treatment, with 93.33% of these patients using garlic in its whole and fresh form. Meanwhile, 6.66% of patients use dried stems, with 73.33% using these dried stems in infusion, and 13.33% using them in decoction.

- ***Curcuma longa.***

The results show that 08 out of the 50 patients with CRC use turmeric as a curative treatment, which represents a frequency of 14.55% of all plants used by the surveyed population. Turmeric is used in its fresh form by 37.5% of patients and in its dried form by 62.50%. As for the most used preparation, it is infusion (62.5%) followed by decoction (37.5%). Patients who use the root represent 87.5%, while 12.5% use the whole plant.

- ***Zingiber officinale***

The results show that 08 out of the 50 patients with CRC use ginger as a preventive treatment, which represents a frequency of 14.55% of the surveyed population. Ginger is used in its whole and fresh form by 37.50% of patients, while 62.5% of patients use it in powder form and dried. As for the most used preparation, it is decoction (75%) followed by infusion (25%).

- ***Linumusitatissimum***

The results show that 05 out of the 50 surveyed patients use flax seeds as a curative treatment against CRC, which represents a frequency of 09.09%. 80% of these patients use dried flax seeds in their intact form, while the remaining 20% use them in powder form. As for the most used preparation, it is infusion (60%) followed by decoction and maceration (20% each).

- ***Ephedraalata***

This survey shows that this plant is used by 05 patients with CRC, with a frequency of 09.09%. These patients use the whole dried plant as a curative treatment, with 80% using it in its dried form and 20% in powder form. The most used preparation is decoction and maceration (40% each) followed by infusion (20%).

- ***Camellia sinensis***

The results show that 02 out of the 50 patients with CRC use green tea as a curative treatment, which represents a frequency of 03.63%. 100% of these patients use dried or fresh leaves of green tea, in decoction, with a percentage of 50% each.

- ***Salviaofficinalis***

The results show that the frequency of use of this plant is 03.63%, used by only 02 patients as a curative and preventive treatment (50% each). One of these two patients uses dried leaves in decoction, while the other uses fresh leaves in infusion.

- ***Annonamuricata***

The results show that this plant is used by 02 people with a frequency of 03.63%. Graviola is used as a curative treatment, representing a percentage of 04% of the surveyed population. Graviolaisused as fresh fruit, consumeddirectly.

- ***Medicagosativa***

The results show that the frequency is 05.45%, used by 03 people with CRC who use clover (Pristim) as a curative and preventive treatment, with 66.67% of these patients using dried roots in decoction. While 33.33% of patients use the powder of dried leaves mixed with Aquilariamalaccensis, prepared in Euphorbia honey (Daghmous).

- ***Aquilariamalaccensis***

The results show that 03 out of the 50 surveyed patients use oud ghriss as a curative treatment, which represents a frequency of 05.45%, with 66.67% of these patients using dried roots in decoction. While 33.33% of patients use the powder of dried leaves mixed with Medicago sativa, prepared in Euphorbia honey (Daghmous).

- ***Glycyrrhizaglabra***

The results show that only one patient with CRC uses licorice as a curative treatment, representing a percentage of 01.83% of the surveyed population. This patient usesdriedlicoriceroots in decoction.

- ***Foeniculumvulgare***

This survey shows that only one patient uses fennel seeds as a curative treatment, representing a percentage of 01.83% of the surveyed population. These dried seeds are prepared in decoction.

Dosage and treatment period.

The results show that patients with CRC use plant-based treatment once a day at a percentage of 60%, twice a day at 34%, and three times a day at 06% of the surveyed population (Fig. 29). However, the treatment period is three months for 12%, six months for 20%, 12 months for 24%, and other periods ranging from one month to signs of healing.

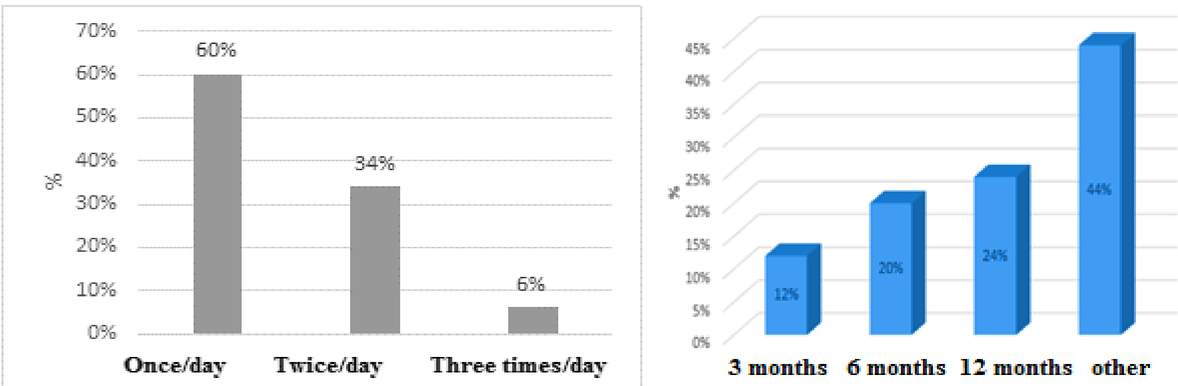


Fig. 29: Dosage and treatment period with plant-based remedies.

Patients' opinions

Among the interviewed patients, 98% of the patients were satisfied with the results obtained and they want to advise CRC patients to use herbal medicine as a complementary treatment to chemotherapy and surgery. This explains the effectiveness of the plants used by these patients. While 02% of the patients do not want to advise CRC patients to use herbal remedies, which explains that the plants used by this population were not effective themselves or the chosen preparation was not useful (Fig. 30).

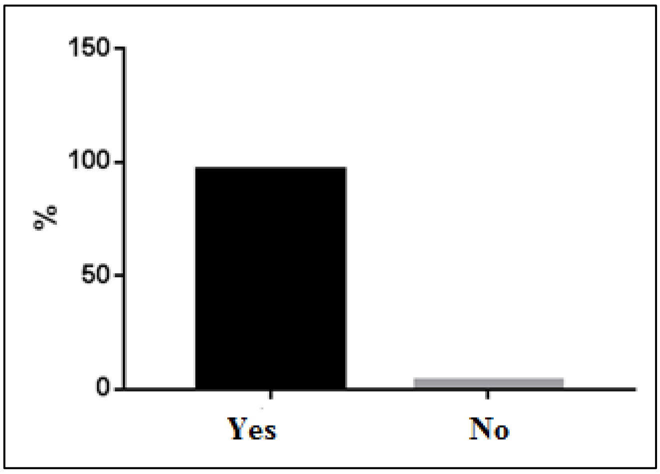


Fig. 30: Percentage of patient satisfaction with CRC phytotherapy.

The results obtained in this survey are already proven scientifically, as indicated in the first chapter concerning CRC-related data and the second chapter on CRC phytotherapy. Although the evidence regarding phytotherapy for colorectal cancer is promising, it is important to note that most studies have been conducted in the laboratory or on animal models. Additional clinical trials are needed to evaluate the effectiveness and safety of these plant compounds in humans. Furthermore, phytotherapy should be used in conjunction with conventional treatments under the supervision of healthcare professionals. It is important to consider potential interactions with medications and individual patient characteristics when integrating phytotherapy into colorectal cancer treatment plans.

Conclusion

Phytotherapy is one of the ancient medical sciences, used for the treatment of numerous diseases and cancers with few side effects. Colorectal cancer is a major public health problem due to its mortality. This work is devoted to the bibliographic and ethnobotanical study of the anticancer effect of certain medicinal plants in the case of CRC. The results show that phytotherapy reveals promising results as a complementary or alternative approach in the treatment of colorectal cancer, and that the most commonly used plants, whether scientifically or traditionally, are Garlic (Allium sativum), Turmeric (Curcuma longa), Ginger (Zingiberofficinale), Sage (Salvia officinalis), Andla (Ephedra alata), Green tea (Camellia sinensis), Oud ghriss (Aquilariamalaccensis), Fennel seed (Foeniculumvulgare Mill), Licorice (Glycyrrhizaglabra), Pristim (Medicago sativa), Flaxseed (Linumusitatissimum), and Graviola (Annona Muricata). Scientifically, these plants and their Active compounds exert an anticancer effect in the case of CRC by using two major mechanisms: induction of apoptosis and inhibition of cancer cell proliferation, using several molecular signaling pathways.

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