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Andrographolide And Its Analogues in Colon Cancer (Anti-tumor Activity)

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Abstract

The large intestine (colon), where colorectal cancer, also known as colon cancer, first appears, is a cancer that greatly affects death rates across the world. Although the present methods of treating colon cancer largely aim to reduce symptoms, neither a cure nor a reversal of the disease's course are offered. Finding novel therapeutics that are efficient, conclusive, and toxic-free is therefore urgently needed. Examining phytochemical, which have drawn interest as substitute and superior remedies for treating a variety of illnesses, is one intriguing strategy. Plants are abound in phytochemical, which are secondary compounds with biological activity but no nutritional value. Among these substances, Andrographolide and its derivatives derived from the medicinal plant Andrographis paniculata have been widely employed in different traditional medicinal systems for treating various diseases, including cardiovascular conditions.

In this review, we look into the in-vivo and in-vitro anticancer activity of Andrographolide and its derivatives. Through tailored drug development techniques that not only concentrate on conventional routes but also incorporate particular signaling pathways, Andrographolide's demonstrate their anticancer benefits.

Along with the suppression of the P13K/Akt pathway, which is linked to inflammation and activation the Nrf-2/HO-1 system, which is linked to antioxidant processes, these pathways include Wnt/-catenin, Hippo, Hedgehog,NF-B, STAT, p53 and P13-K/AKT/ERK. Through anti-arrhythmic, anti-hypertensive, anti-inflammatory and antioxidant mechanisms, animal studies have demonstrated that Andrographolide and its derivatives are effective against cancer. As a result, Andrographolide and its derivatives may prove to be excellent candidates for the creation of brand-new colorectal cancer treatment compounds. In the near future, more investigation and study in this area might result in viable therapy possibilities.

1. Introduction

Colon cancer, sometimes referred to as colorectal cancer, first manifests itself in the large intestine (colon), the final organ of the digestive system. Although it mostly affects elderly folks, it may happen to anybody. Noncancerous (benign) polyps that occur on the colon's inner lining frequently signal the beginning of colon cancer. Some of these polyps might develop into colon cancer in the future.

Polyps are often tiny and don't always produce obvious symptoms. To prevent colon cancer, routine screening tests are suggested to identify and remove polyps before they transform into cancer. The condition can be managed with a variety of treatments if colon cancer does manifest. These consist of operations, radiation treatment, and medication therapies such chemotherapy, targeted therapy, and immunotherapy.

It's crucial to understand that since rectal cancer develops in the rectum, the phrase "colorectal cancer" refers to both colon and rectal cancer.

SYMPTOMS

There are several distinct colon cancer symptoms, however some people, especially in the early stages of the disease, may not experience any. However, if symptoms do manifest, they may include:

- Constipation, diarrhoea, or other persistent changes in bowel habits, as well as adjustments to the consistency of the stool.

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• Blood in the stool or bleeding from the rectum.

• Constant stomach discomfort including pain, gas, or cramps.

• A sense that the bowels are not completely emptying.

• Weakness or exhaustion.

• Unaccounted-for weight reduction.

It's important to keep in mind that the specific symptoms experienced may vary depending on the size and location of the cancer inside the large intestine.

CAUSES

Medical experts say it's still unclear what causes the majority of colon cancers. Typically, healthy colonic cells receive DNA alterations that lead to the development of colon cancer. A collection of instructions discovered in DNA controls how a cell works.

To maintain the body's correct functioning, healthy cells generally divide and grow in an organized manner. On the other hand, when a cell's DNA is harmed and it develops into cancer, the cells keep dividing even when new cells are not required. A tumor is produced when these cells accumulate over time.

The malignant cells can penetrate and obliterate neighbouring healthy tissues as the disease spreads. Metastasis is the ability of cancer cells to travel to various parts of the body and form new growths.

RISK FACTORS (2,3,4)

Your chance of acquiring colon cancer may rise due to a number of variables, such as:

1. Elderly: Although colorectal cancer can develop at any group of age, it is more frequently detected in those over 50. Though the precise causes are still unknown, there has been a noticeable rise in colon cancer rates among those under 50.

2. African-American Race: In comparison to people of other races, African-Americans have a greater risk of colorectal cancer.

3. Patient History: If any one ever had noncancerous colon polyps / colon cancer, your chance of getting it again is increased.

4. Inflammation in Intestine: Colorectal cancer risk can be raised by long-term inflammatory conditions of the colon including ulcerative colitis and Crohn's disease.

5. Gene mutations that are handed down through generations and cause certain genetic syndromes can dramatically raise the risk of colon cancer. Lynch syndrome, also known as familial adenomatous polyposis (FAP), and hereditary nonpolyposis colorectal cancer (HNPCC), are the two most common genetic conditions associated with a higher risk of colon cancer.

6. Family History of Colon Cancer: Your chance of acquiring colon cancer is increased if you have a blood family who has had colon or rectal cancer. If several family members have had certain malignancies, the risk rises much more.

7. Low-Fiber, High-Fat Diet: Although research has produced conflicting findings, a diet that has a high fat and calorie content but little fiber, which is frequently associated with a Western diet, may raise the risk of colon and rectal cancers. According to several research, Colon cancer risk is higher in those who consume a lot of processed and red meat in their diets.

8. Sedentary Lifestyle: Colon cancer risk is increased by inactivity and a lack of regular exercise.

9. Diabetes: Colon cancer risk is greater in people who have diabetes or insulin resistance.

10. Obesity: Obese people are more likely than people of a healthy weight to acquire colon cancer.

11. Smoking: Colon cancer risk has been associated with cigarette use.

12. Alcohol: Drinking excessive amounts of alcohol is linked to a higher colon cancer risk.

13. Radiation: Previous abdominal radiation to used to treat tumour in the past may be the course of colon cancer.

PREVENTION

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Starting around the age of 45, screening for colon cancer is advised for people with an average risk. Thoughts about screening should be made early in life for individuals who are at a greater risk, such as those who have a family history of colon cancer. There are several screening options, each having advantages and disadvantages of its own. The best tests for your circumstance should be decided after discussing these possibilities with your doctor.

You may modify your lifestyle to lower the risk of colon cancer by screening. Think about following actions:

1. Include a Variety of Fruits, veggies, and Whole Grain Products in Your Diet: Make sure that your diet contains a variety of fruits, veggies, and whole grains. These foods provide important antioxidants, fibre, vitamins, and minerals that may help prevent cancer. To get a variety of nutrients, aim for a diversity of options.

2. Consume Alcohol Moderately: If you decide to consume alcohol, it is recommended that you keep your intake to a minimum. This entails a daily limit of one drink for females and two for males.

3. Quit Smoking: Talk to your doctor about successful smoking cessation methods that could be right for you.

4. Exercise Regularly: Make an effort to work out daily. Aim for minimum half hours of exercise every day. If you are not active, start it slowly and raise your exercise level over time. Consult your doctor before starting any workout programme.

5. Weight: if you have a healthy weight, concentrate on keeping it that way by eating a balanced diet and getting regular exercise. Consult your doctor for advice on healthy weight loss techniques if you need to lose weight. By increasing physical activity and consuming less calories, aim for progressive weight loss.

You can actively lower your chance of getting colon cancer by making these lifestyle changes.

Drug Targets in Colon Cancer (5-11)

Certain colon or rectal cancers can be treated with medications that particularly target the development of blood vessels or vascular endothelial growth factor (VEGF). These medications consist of:

1. Bevacizumab (Avastin)

2. Ramucirumab (Cyramza)

3. Ziv-aflibercept (Zaltrap)

Every two or three weeks, these drugs are given intravenously (IV) in infusions, frequently in conjunction with chemotherapy. These medications have the potential to increase the life expectancy of people with advanced colon or rectal malignancies when used in combination with chemotherapy.

Drugs that target VEGF may have the following adverse effects:

1 High blood pressure is one.

2. a state of extreme exhaustion

3. Bleeding

4. Low white blood cell counts increase the risk of infection

5. Headaches

5. Mouth ulcers

7. Appetite loss

8. Diarrhea

Blood clots, severe bleeding, intestinal perforations, heart difficulties, renal problems, and sluggish wound healing are just a few of the uncommon but potentially dangerous adverse effects. A serious infection from a colon perforation may call for surgical treatment. An allergic reaction that occurs while the infusion, that can result in breathing issues and low blood pressure, is another unusual but important side effect.

The epidermal growth factor receptor (EGFR), which has undergone modifications, is the focus of another family of medications. These medications, which include Cetuximab (Erbitux) and Panitumumab (Vectibix), are normally given intravenously once every week or every other week. In colorectal tumors caused by Mutation in KRAS, NRAS or BRAF genes they are often ineffective.

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Doctors frequently test tumour for these gene alterations prior to therapy and they exclusively provide these drugs to people without these mutations. The exception is when cetuximab is used with the BRAF inhibitor encorafenib, though since it has shown promise in prolonging life expectancy in advanced colon cancer patients, among those who have any of these genetic mutations too.

Drugs that target EGFR may have the following adverse effects:

1. Skin issues: such as a rash on the chest and face that resembles acne, which can occasionally cause infections. It could be required to treat the rash and related illnesses using antibiotic creams or ointments. The appearance of this rash frequently denotes a favourable response to therapy.

2. Headache

3. Tiredness

4. Fever

5. Diarrhea

Similar to VEG F-targeting medications, EGFR-targeting therapies can cause an allergic response during the infusion that can cause breathing problems and low blood pressure. Prior to therapy, medication could be given to lessen this.

Occasionally, the BRAF gene will alter (mutate) in colorectal tumour. The presence of an aberrant BRAF gene is checked in people with colorectal cancer that has spread. BRAF inhibitors specifically target the faulty BRAF protein, such as Encorafenib (Braftovi). Encorafenib can reduce tumour or inhibit spread of colon cancer in certain patient with metastatic disease when taken with cetuximab, potentially prolonging their life. Encorafenib is given once day orally as tablets or capsules.

Encorafenib with cetuximab side effects are frequently Diarrhoea, rash, loss of appetite, stomach discomfort, joint pain, tiredness, and nausea are some of the symptoms. BRAF inhibitor users occasionally experience the development of fresh squamous cell skin malignancies, which are routinely treated surgically. It's crucial to have routine skin exams both during and after therapy.

Andrographolide And Its Analogue's Role in Cancer and Other Disease

paniculata, a plant belonging to the Acanthaceae family, is used medicinally and may be found in Sri Lanka, China, India, and other South Asian countries. The "king of bitters" is how people usually refer to it, and in India, it is called Kalmegh. A. paniculata has a wide variety of defence mechanisms, including cyanogenesis, phytohormone activation, cell wall lignification, and alteration of secondary metabolites, to ward off pathogens and pests. It has a long history of medical use in both Indian and Western medicine. In recent years, the risk of cancer and its prevention have been linked to natural treatments and dietary elements. A. paniculata has several significant pharmacological qualities like hepatoprotective, antimicrobial, anti-inflammatory and anti-thrombotic action. The treatment of animal ailments has also involved its use.

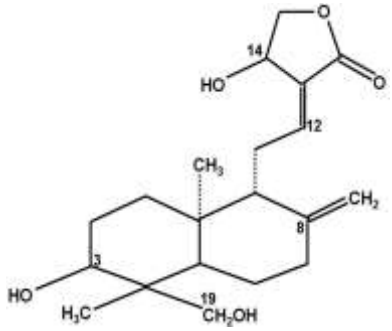

Figure 1. Andrographolide has a labdane diterpenoid framework for its chemical structure. It is Andrographis paniculata's main bioactive substance. A -alkylidene -butyrolactone moiety, two olefin bonds at positions 8(17) and 12(13), and three hydroxyl groups at C-3, C-14, and C-19 define Andrographolide.

In place of antibiotics, A. paniculata and Andrographolide have been used to treat common illnesses such respiratory infections and diarrhoea. The pharmacological action of Andrographolide and A. paniculata plant extract have both thoroughly investigated in vitro and in vivo. A. paniculata's ethanolic extract has shown antiviral effectiveness against type 1 of the herpes simplex virus. This plant's usage in the treatment of neoplasms has been documented in the classical Ayurveda. The main phytochemical of A. paniculata and Andrographolide,

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has a bitter flavour and regarded as one of the most significant natural product chemicals.

Andrographolide has been proven in studies to have hepatoprotective qualities and to be somewhat more active than the well-known hepatoprotective medication silymarin. It has received great praise for its curative effects in treating human cancer, inflammation, common colds, and liver diseases. Along with other disorders, Andrographolide has shown effectiveness in treating allergic responses, hemorrhagic lesions, and central nervous system dysfunction.

A.paniculata has been a key ingredient in a number of pharmaceutical products, including as formulations for antipyretic, anti-inflammatory, hepatoprotective, and immunostimulant agent, according to the Indian Pharmacopoeia neoAndrographolide and 14-deoxy-11, 12-didehydroAndrographolide are examples of Andrographolide derivatives that have been used in traditional remedies to treat cancer, diabetes, renal problems, hepatitis, and HIV. It has been acknowledged that Andrographolide and its analogues represent a new type of anti-inflammatory and anticancer medications.

We have gathered a variety of A. paniculata characteristics in this review, with an emphasis on Andrographolide's effects on cancer and the underlying processes at play. In order to clarify the effects of Andrographolide and its derivatives, particularly in connection to human malignancies, we have thoroughly investigated and evaluated the literature. The significance of Andrographolide in human cancer has been the major topic of our discussion, along with its effects on cell development and death processes and potential future applications in the fight against cancer.

PHYTOCHEMISTRY OF Andrographolide AND ANALOGUES

The A. paniculata plant is a noteworthy plant in the field of phytopharmaceuticals due to the secondary metabolites discovered in it. Andrographolide, neoAndrographolide, and deoxyAndrographolide are only a few of the diterpenoid and diterpenoid glycosides with comparable carbon skeletons that are present in the plant. A 14-deoxyandro-grapholide, a 14-deoxy11,12-didehydroAndrographolide, stigmasterol, andrographiside , andrographan, homoAndrographolide, andrographosterin, and andrographon are some of the other significant phytochemicals found in the plant. The most prevalent phytochemical in A. paniculate, Andrographolide is extremely bitter and mostly found in the plant's leaves. Andrographolide has a lactone function, an a-alkylidene c-butyrolactone moiety, two olefin bonds (C-3, C-14, and C-19), three hydroxyls at C-3, C-14, and three olefin bonds (C-8, C-13). In addition, the plant includes a significant amount of xanthones, stigmasterols, and labdane diterpenoids.

Systematic chemical investigations on A. paniculate and its components have been conducted by several researchers. A couple of the 19 Andrographolide analogues studied for structure-activity connections have stronger cytotoxic effects than the original molecule. In breast cancer cells, the 14-deoxy-11, 12-didehyroandrogrpholide gene controls genes involved in the cell cycle, promotes cell cycle arrest, and may result in autophagic morphology. Although a wide variety of pharmacological effects of Andrographolide and its derivatives have been established by researchers, little is known about its functional activity in a number of human disorders, including cancer.

Hepatoprotective

The hepatoprotective properties of Andrographolide and its derivatives, which may be used to treat different forms of liver injury, are well known. The scientific community has paid close attention to this property. The plant's main anti-hepatotoxic compound, Andrographolide, has demonstrated impressive protective properties in vivo against anti-hepatotoxic brought on by chemicals including carbon tetra-chloride (CCl4), D-galactosamine, paracetamol, and ethanol. In fact, Andrographolide has shown to be more efficacious than silymarin, the traditional hepatoprotective drug.

Recent research have developed 10 aqueous-soluble Andrographolide derivatives that demonstrate hepatoprotective action against CCl4-induced liver damage in mice, despite the fact that Andrographolide's poor solubility in water has presented difficulties in clinical use. Andrographolide has been shown to be efficient as a hepatoprotective and hepato-stimulating drug against a variety of

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Journal of Coastal Life Medicine

hepatotoxins in several trials. Andrographolide has been proven to successfully counteract hepatotoxicity brought on by a variety of toxins by modulating liver function enzymes and activating antioxidant agent in the liver.

Analogues of Andrographolide from A. paniculate have give hepatoprotective activity efficacy in both *in-vitro* and *in-vivo* models in animal investigations. By giving the plant's aerial parts' methanol extract to mice and rats, researchers were able to minimise CCl4-induced hepatotoxicity and reverse histological liver damage. Andrographolide was administered intraperitoneally, and this reduced the rise in liver enzyme activity brought on by CCl4. Additionally, giving ethanol-treated mice an aqueous extract of the plant's aerial portions reduced the activity of liver function enzymes and attenuated histological liver alterations.

Together, these results show that Andrographolide has strong hepatoprotective properties without any known negative effects, making it an exciting therapeutic option for liver therapy and protection.

Anti platelet aggregation

In thrombosis, wound healing, and homoeostasis, platelets are essential. The effects of Andrographolide and its equivalents on platelets have been shown to promote apoptosis. According to studies, Andrographolide covalently changes p50's decreased cysteine 62, inactivating NF-B in inflammatory and neointimal hyperplasia conditions. Tissue factor, an essential component of blood coagulation, is transcriptionally regulated, and NF-B is essential for tissue factor expression. In particular in the aetiology of deep vein thrombosis, P50 is critical for tissue factor modulation and its interaction with NF-B at the human tissue factor promoter site is important. Since p50 is specifically inhibited by Andrographolide, there is a decrease in venous thrombosis.

Blood clots must be broken up through a process called fibrinolysis in order to prevent cardiovascular disease. When given intravenously to hypertensive rats, a study indicated that an extract of A. paniculate has anti hypertensive effects. By preventing nor adrenaline from contracting smooth muscle walls in blood vessels, Andrographolide has anti-hypertensive effects. Because nor adrenaline causes blood vessels to contract, Andrographolide's inhibitory effect encourages blood flow and oxygen delivery. These results emphasise the potential of Andrographolide in venous thrombosis prevention and perhaps treatment. Furthermore highlighting its potential therapeutic use, Andrographolide may potentially interact with angiogenesis or vasculogenesis signalling pathways in cancer metastasis.

Anti-inflammation

Due to the fact that Andrographolide and its derivatives have anti-inflammatory properties, they have become important in traditional medicine. It has been demonstrated that they inhibit NF-κB signalling pathways and reduce the production of chemokines, cytokines and lipid mediators. Andrographolide reduces inflammation in human umbilical vein endothelial cells (HUVECs) via blocking the PI3K/Akt pathway and targets that are activated downstream of NF-κB.

According to research, Andrographolide prevents the activation of the MEK1/2, ERK1/2 (p42/p44), and Akt signalling pathways, which is what reduces macrophages' chemo-tactic movement. Additionally, it prevents RAW264.7 cells stimulated with lipopolysaccharide (LPS) from producing the enzymes inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), which prevents the expression of NF-κB. Inhibiting NF-κB activation as a result of Andrographolide's modification of decreased cysteine in p50's oligonucleotide binding pocket may help cure oral squamous cell cancer.

Additionally, Andrographolide inhibits the mRNA expression of the suppressors of cytokine signalling (SOCS1and SOCS3) which inhibits apoptosis signalling and inhibits the activation of mitochondrial membrane potential. Pro-inflammatory mediators such TNF-α, GM-CSF, IL1β, IL-6, IL-8, iNOS, NO and COX-2 are prevented from being produced. Endothelial-monocyte adhesion is inhibited by Andrographolide because it down-regulates the expression of adhesion molecules (E-Selectin and ICAM-1).

Additionally, Andrographolide decreases macrophage-1 antigen expression, neutrophil adhesion and activation brought on by N-formylmethionyl-leucyl-phenylalanine, and NO and ROS generation.

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Journal of Coastal Life Medicine

Andrographolide serves a crucial therapeutic function in avoiding tissue damage brought on by oxidative stress by suppressing iNOS expression and lowering NO generation.

Andrographolide has also been demonstrated to boost both antigen-specific and nonspecific immunological responses, which in turn stimulates the immune system. The lymphatic system is stimulated, lymphocyte production is encouraged, and interferon/cytokines, which have antiviral qualities, are released. Andrographolide is effective against a variety of infectious pathogens and neoplastic processes because of these immune-stimulating qualities.

In conclusion, some cellular signaling systems are how Andrographolide exerts its anti-inflammatory effects. Its capacity to control diverse immunological and inflammatory pathways emphasizes its therapeutic promise in a range of cellular diseases.

Anticancer (Colon cancer)

Cancer is a serious worldwide health issue that is characterized by unchecked cell proliferation, cell death evasion, angiogenesis, invasion, and metastasis. The often inflamed and highly active In redox processes, the cancer micro environment is crucial to the development and spread of malignancies. The use of natural materials as possible sources of chemotherapeutic drugs with promising anti-tumor properties has gained popularity. Recent methods for developing anticancer drugs specifically target cancer-related signalling pathways such as Wnt/β-catenin, Hippo, Hedgehog, STAT, p53, NF-κB and ERK/P13K/AKT.

Leukaemia, breast, lung, and melanoma cell lines are just a few of the cancers that Andrographolide and its analogues have shown to be able to stop from proliferating. By deactivating the AKT and ERK signaling pathways and preventing the activity of matrix metalloproteinase 2 (MMP2), Andrographolide demonstrates a variety of characteristics. As a result, it inhibits colon cancer cells' capacity for invasion. It has been shown that Andrographolide alters these pathways via altering genes associated to cell cycle regulation, adhesion-related signaling, and apoptosis. MMPs and its regulatory processes have proven to be intriguing targets for the creation of anticancer drugs.

Additionally, Andrographolide influences the PI3K/AKT signaling pathway's down regulation and inhibits the c-Jun/c-Fos (AP-1 heterodimer complex), which prevents cell invasion and migration as well as the production of MMP-7. Additionally, it inhibits human umbilical vein endothelial cells' (HUVECs) MMP-2 and MMP-9 activities, which are crucial for angiogenesis. The molecular underpinning for Andrographolide's anticancer effect is also provided by the discovery that it inhibits heat shock protein 90 (Hsp90) function and decreases the amounts of Hsp90 client proteins.

Additionally, the CYP1A superfamily gene, which is implicated in the activation of carcinogenic chemicals, is controlled by Andrographolide and its derivatives. On the expression of the aryl hydrocarbon receptor, Andrographolide acts as an antagonist ligand and is involved in the metabolism of heterocyclic amines and carcinogenic amino acids.

Depending on the particular type of cancer cells present both *in-vitro* and *in-vivo*, the processes behind Andrographolide's anticancer effect may change. The potential of Andrographolide and its analogues as prospective anticancer medicines with varied modes of action is highlighted by these research.

Cytotoxicity

Andrographolide and its analogues have cytotoxic effects on both cancerous and non-cancerous cell lines, depending on the dosage and length of therapy. Even while the term "cytotoxicity" normally refers to cell toxicity, there is a particular need for toxicity that specifically targets cancer cells. According to research, Andrographolide has no impact on healthy liver cells (L-02), however it has lethal effects on human hepatoma cell lines (HepG2). Additionally, research has shown that Andrographolide and its analogues increase the levels of autiphagy marker in a range of cancer cell line and probably prevent the maturation and degradation phases of autophagic flux (63). Significant cytotoxic action has been shown for Andrographolide against the KB (Human Epidermoid Leukaemia) and P388 (Lymphocytic Leukaemia) cell lines. Andrographolide induces autophagic cell death by modifying the potential of the mitochondrial membrane and increasing the levels of reactive oxygen species (ROS), according to studies on the potential cytotoxic effects of the compound on human

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liver cancer cells. The increase of LC3-II protein, the creation of autophagosomes and the production of puncta GFP LC3 were all indicators of the Andrographolide-induced autophagy (43). Another Andrographolide compound, Andrographolide-lipoic acid, also demonstrated anticancer activity by inducing mortality in patient leukaemia K562 cells by ROS-dependent DNA damage(64). Andrographolide has been shown to have cytotoxic and antiproliferative properties in recent studies (65). The blood-brain barrier can be broken by Andrographolide, which can then build up in the brain. Thus, Andrographolide promotes cell cycle arrest in the G2/M phase and down-regulator cdk1, cdc25proteins, as well as lowers the activity of P13/Akt signalling with reduced expression of P13K,pAkt and pmTOR (65). This was demonstrated in a research on glioblastoma cells.

A. paniculata's ethanolic extract yielded the chemical 14-deoxyAndrographolide, which was four times as cytotoxic than the water extract (66). When compared to Andrographolide, the majority of the substances studied as Andrographolide analogues showed considerable cytotoxicity. The underlying mechanism for the cytotoxicity against cancer cells was the oxidation of the Andrographolide's C-19 hydroxyl group to generate a carboxyl group, which then esterified into a carboxylic acid (67).

Apoptosis induction

Apoptosis is a term for the evolutionary conserved intracellular process that mediates programmed cell death. Apoptosis has been linked to cancer in recent years due to its function in the growth and spread of the disease. Apoptosis is frequently resistant in cancer cells. Recently, both organic and synthetic anticancer compounds have been created to reactivate apoptotic pathways, increasing the susceptibility of cancer cells to apoptosis and enabling cytotoxic medications to trigger apoptosis at low dosages (51–53, 68). According to reports, Andrographolide and its analogues can cause apoptosis in a number of cancer forms. In human neuroblastoma cells, Andrographolide has been shown to activate caspase-3 and p53, suppress NF-κB activity, and cause cell death (69).

A key transcription factor that control cell proliferation and death is NF-κB (70). In the human hepatocellular carcinoma (HCC) cell line SMMC-7721, Andrographolide and fluorouracil (5-FU) therapy boosted apoptosis and reduced p53. As a result, apoptosis was reactivated by altering the Bax conformation, activating caspase-3,-8 and -9, destroying the potential of the mitochontdrial membrane and increasing the release of cytochrome c (71). Andrographolide was suggested as a possible cancer treatment possibility in a research (72). The phosphorylation of p53 by Andrographolide led to the transcriptional up-regulation of deth receptor 4 (DR4). Through tumour necrosis factor- ralated apoptosis including ligand (TRAIL), this activation caused apoptosis in TRAIL resistant cells, Andrographolide increased DR4-mediated TRAIL induced apoptosis (72).

Epidermal growth factor receptors (EGFRs) and transferrin receptors (TfRs) were down-regulated on the cell surface and degraded as a result of treatment with Andrographolide in T-47D mammary cells (73). Andrographolide caused apoptotic cell death and reduced the production of IL6 (This is essential for prostate cancer development). As a result, Andrographolide may be used as a therapeutic drug to treat both androgen stimulated prostate cancer and castration resistant prostate cancer (74). A new mechanism and a prospective chemotherapeutic target for different cancers is the modification of DNA topoisomerase II. A modest dosage of an analogue of Andrographolide inhibited DNA topoisomerase II and caused apoptosis in cholangiocarcinoma (75).

In several cancer cell lines, Andrographolide caused apoptosis and inhibited cancer cell proliferation, however it is yet unclear which cell's receptor trafficking is specifically impacted by the compound.

Cell cycle arrest

The discovery that andrographis and its constituents can impede a cell's ability to continue through its cell cycle is crucial for the creation of anticancer treatments. By reducing endothelial cell motility and tumor endothelial cell contact, Andrographolide has been found the impact on human brest cancer cells. By stopping the cell cycle at the G2/M phase and indiucing apoptosis via caspase independent route, it slows the development of tumours (76). Similar investigations have found that Andrographolide stops the devlopment of human hepaytoma cells by causing late apoptosis and stopping them at the G2/M phase

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of cell cycle. Andrographolide decreases superoxide radicals while increasing hydroxyl peroxide (H2O2) generation and lowering glutathione stimulating hormone (GSH) levels in mitochondria (61).

By reducing the expression of cell cycle related proteins and boosting the expression of cell cycle inhibitory proteins including p16, p21 and p53, Andrographolide has an antiproliferative action in colon cancer cells (77). As a result, it suppresses Rb phosphorylation and lowers the amounts of cell cycle regulatory proteins like cyclin A, cyclin D, CDK4 and CDK2, which are necessary for G1-S tarnsition. Most human colon cancer, Lovo cells are arrested in the G1 phase by treating with Andrographolide due to the induction of p27 expression and suppression of CDK4 in human tumar cell lines (77). Some analogues of Andrographolide, including 3A.1 19-tert butyldiphenylsily, 1,8,17 epoxy Andrographolide, activate caspase-3 while down-regulating CDK6, COX-2 and cyclin D1 protein expression. They are also capable of inducing apoptosis in initial malignant tumours of bile duct epithelial cells by suppressing DNA topoisomerase II α expression (78).

Anti tumor

Utilizing their distinct anticancer mechanisms, Andrographolide and its analogues have been studied for their potential use in cancer chemo prevention. With little negative effects on non-cancerous cells, Andrographolide has been effectively used as an anti neoplastic medication in cancer treatment. By encapsulating Andrographolide in PLGA nanoparticles with an extra chitosan coating, non-toxic and delivery-efficient Andrographolide nanoparticles were created to increase their anticancer activity. These nanoparticles showed improved anticancer activity in Ehrlich ascites carcinoma mice model and human breast cancer cells (79). Different Andrographolide formulations in nanoparticles form demonstrated better anticancer activities and improved chemotherapeutic efficacy by causing G1 phase cell cycle arrest and apoptosis in the breast cancer MCF7 cell line. *In-vivo* tests verified that Andrographolide nanoparticles reduced tumour weight more effectively than Andrographolide alone (79). The anticancer preparation Andrographolide nanoparticles seems to be both secure and effective.

As a result of the PI3K/AKT signalling pathway being downregulated by Andrographolide therapy, hypoxia inducible factor 1α (HIF-1α) expression is reduced through ubiquitin-dependent degradation (80). Non small cell lung cancer (NSCLC)and A549 cells both depend on HIF-1α to promote tumour development. Treatment with Andrographolide inhibited HIF-1α, decreased VEGF and enhanced the expression of prolyl hydroxylase and hydroxyl-HIF-1α (80). These results emphasise the potential of Andrographolide as a chemotherapeutic or anti-angiogenesis medication for the treatment of NSCLC.

Another investigation revealed Andrographolide's protective effects against cyclophosphamide (CTX)-induced urothelial damage (81). Mice (swiss albino) pretreated with Andrographolide and A. paniculata extract showed a substantial reduction in CTX-induced urothelial damage. The pro-inflammatory cytokine TNF-α, which is increased following CTX treatment, was reduced by Andrographolide. The levels of IL-2 and IFN-γ which are decreased by CTX therapy, were also elevated by Andrographolide (81).

By attaching to momentary Kirsten-Ras (K-Ras) pockets, Andrographolide may function as a ligand to impede GDP-GTP exchange. As a result, it lessens wild typeK-Ras's responseto acute EGF stimulation in term of GTP loading. Through its binding to Ras, Andrographolide also inhibits the oncogenic mutant K-RasG12V from transmitting signals (82). This shows the effectiveness of Andrographolide as a method to stop the action of Ras' oncogenic mutation.

Dehydro-Andrographolide, one of Andrographolide's derivatives, has been touted as a novel anticancer medication with favourable intestinal absorption and metabolic stability. Although dehydro-Andrographolide absorbs quickly in the colon, there have been no detectable responses in intestinal perfusates. As a result of Andrographolide, many amino analogues (β-amino γ-butyrolactone) have been produced with great stereoselectivity and good yield. As evidence of their potential as powerful anticancer drugs, these amino analogues demonstrated cytotoxic activities to six types of cancer cell lines (83).

Additionally, Andrographolide therapy for neuroblastoma has demonstrated enhanced cytotoxicity when combined with cisplatin or doxorubicin (69). These results highlight the

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CODEN: JCLMC4
Journal of Coastal Life Medicine

anticancer capabilities of Andrographolide and its analogues, both individually and together, andoffer the possibility for the creation of innovative treatment approches.

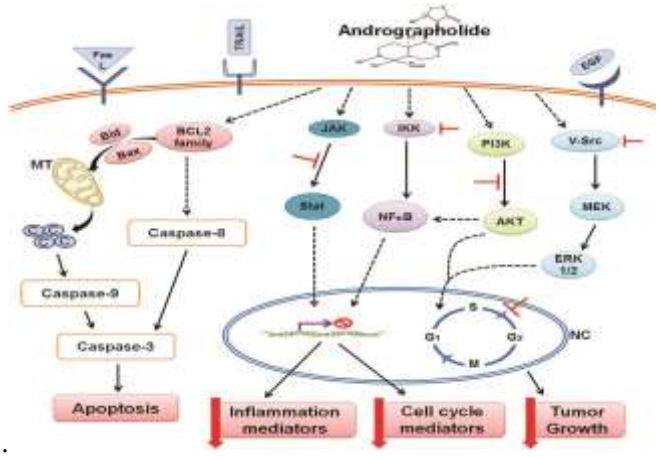

Figure 2. Diagrammatic representation of Andrographolide's cancer treatment mechanism is provided. Andrographolide attach to multiple receptor binding sites on cell membranes and then transduce certain signalling events that cause a number of different phenomena such as the induction of apoptosis, the suppression of inflammation, the cessation of the cell cycle and the slowing of cancer development.

2. Conclusion

In conclusion, colorectal cancer has a high death rate worldwide, with few effective treatments available, along with side effects. Thus, there is a need for the creation of novel, all-natural medications that can successfully treat colorectal cancer. The anticancer properties of Andrographolide and its derivatives, especially in colorectal cancer, are the subject of this review. The review gives a summary of the molecular processes that underlie the anticancer actions of Andrographolide and its derivatives, both *in-vitro* (in a lab environment) and *in-vivo* (in animal model). Andrographolide and its derivatives' anti-arrhythmic, anti hypertensive, anti-inflammatory, and antioxidant qualities are thought to be responsible for the anticancer effects.

The work also emphasises two unique methods by which Andrographolides defend against cancer stimulation of Nrf-2/HO-1 pathway and modulation of apoptotic markers. The potential of Andrographolide and its derivatives as alternative therapeutic possibilities for the treatment of colon cancer in the future is discussed in this review.

References

[1] American College of Gastroenterology Chronic Constipation Task Force. "An evidence-based approach to the management of chronic constipation in North America." Official journal of the American College of Gastroenterology| ACG 100 (2005): S1-S4.

[2] Jasperson, K. W., Tuohy, T. M., Neklason, D. W. & Burt, R. W. Hereditary and familial colon cancer. Gastroenterology **138**, 2044–2058 (2010).

[3] American Cancer Society. Atlanta, Georgia: American Cancer Society; 2021. https://www.cancer.org/. Accessed January 22, 2021. [Google Scholar]

[4] Fukuda I, Hizuka N, Murakami Y, et al. Clinical features and therapeutic outcomes of 65 patients with acromegaly at Tokyo Women's Medical University. Intern Med. 2001;40(10):987-992. doi: 10.2169/internalmedicine.40.987. [PubMed] [CrossRef] [Google Scholar]

[5] Kelly SR and Nelson H. Chapter 75 – Cancer of the Rectum. In: Niederhuber JE, Armitage JO, Dorshow JH, Kastan MB, Tepper JE, eds. Abeloff's Clinical Oncology. 6th ed.Philadelphia, Pa. Elsevier: 2020.https://www.cancer.gov/types/colorectal/patient/colorectal-treatment-pdq

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[6] Lawler M, Johnston B, Van Schaeybroeck S, Salto-Tellez M, Wilson R, Dunlop M, and Johnston PG. Chapter 74 – Colorectal Cancer. In: Niederhuber JE, Armitage JO, Dorshow JH, Kastan MB, Tepper JE, eds. Abeloff's Clinical Oncology. 6th ed. Philadelphia, Pa. Elsevier: 2020.

[7] Libutti SK, Saltz LB, Willett CG, and Levine RA. Ch 62 - Cancer of the Colon, Ch 63 - Cancer of the Rectum. In: DeVita VT, Hellman S, Rosenberg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology. 11th ed. Philadelphia, Pa: Lippincott-Williams & Wilkins; 2019.

[8] National Cancer Institute. Physician Data Query (PDQ). ColonRectal Cancer Treatment. 2020. Accessed at https://www.cancer.gov/types/colorectal/patient/colorectal-treatment-pdq on February 19, 2020.

[9] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. V.1.2020. Accessed at https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf on Feb 19, 2020, https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf on Feb 19, 2020.

[10] Riley JM, Cross AW, Paulos CM, et al. The clinical implications of immunogenomics in colorectal cancer: A path for precision medicine. Cancer. 2018 Jan 9.

[11] Wright M, Beaty JS, Ternent CA. Molecular Markers for Colorectal Cancer. Surg Clin North Am. 2017;97(3):683-701.

[12] S. K. Mishra, N. S. Sangwan and R. S. Sangwan: Andrographis paniculata (Kalmegh): a review. Pharmacog Rev, 1(2), 283 (2007)

[13] S. K. Mishra and M. K. Kim: Vitamin A and Cancer Risk. In: Vitamin A and Carotenoids. Ed V. R. Preedy. Royal Society of Chemistry, London (2012)DOI: 10.1039/9781849735506-00485

[14] C. Wiart, K. Kumar, M. Yusof, H. Hamimah, Z. Fauzi and M. Sulaiman: Antiviral properties of ent-labdene diterpenes of Andrographis paniculatanees, inhibitors of herpes simplex virus type 1. Phytother Res, 19(12), 1069-1070 (2005)DOI: 10.1002/ptr.1765

[15] S. Rajagopal, R. A. Kumar, D. S. Deevi, C. Satyanarayana and R. Rajagopalan: Andrographolide, a potential cancer therapeutic agent isolated from Andrographis paniculata. J Exp TherOncol, 3(3), 147-58 (2003) DOI: 10.1046/j.1359-4117.2003.01090.x

[16] W. Deng, R. Nie and J. Liu: Comparison of pharmacological effect of four Andrographolides. Chinese Pharma Bull, 17, 195-198 (1982)

[17] B. Shukla, P. K. Visen, G. K. Patnaik and B. N. Dhawan: Choleretic effect of Andrographolide in rats and guinea pigs. Planta Med, 58(2), 146-9 (1992) DOI: 10.1055/s-2006-961416

[18] A. Puri, R. Saxena, R. P. Saxena, K. C. Saxena, V. Srivastava and J. S. Tandon: Immunostimulant agents from Andrographis paniculata. J Nat Prod, 56(7), 995-9 (1993) DOI: 10.1021/np50097a002.

[19] Valdiani, M. A. Kadir, S. G. Tan, D. Talei, M. P. Abdullah and S. Nikzad: Nain-e Havandi Andrographis paniculata present yesterday, absent today: a plenary review on underutilized herb of Iran's pharmaceutical plants. Mol Biol Rep, 39(5), 5409-24 (2012) DOI: 10.1007/s11033-011-1341-x

[20] J. C. Lim, T. K. Chan, D. S. Ng, S. R. Sagineedu, J. Stanslas and W. S. Wong: Andrographolide and its analogues: versatile bioactive molecules for combating inflammation and cancer. Clin Exp PharmacolPhysiol, 39(3), 300-10 (2012) DOI: 10.1111/j.1440-1681.2011.05633.x

[21] A. Sharma, K. Lal and S. S. Handa: Standardization of the indian crude drug kalmegh by high pressure liquid chromatographic determination of Andrographolide. Phytochem Anal, 3(3), 129-131 (1992) DOI: 10.1002/pca.2800030308

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[22] T. Matsuda, M. Kuroyanagi, S. Sugiyama, K. Umehara, A. Ueno and K. Nishi: Cell differentiation-inducing diterpenes from Andrographis paniculataNees. Chem Pharma Bull, 42(6), 1216-25 (1994) DOI: 10.1248/cpb.42.1216

[23] V. K. Dua, V. P. Ojha, R. Roy, B. C. Joshi, N. Valecha, C. U. Devi, M. C. Bhatnagar, V. P. Sharma and S. K. Subbarao: Antimalarial activity of some xanthones isolated from the roots of Andrographis paniculata. J Ethnopharmacol, 95(2-3), 247-51 (2004) DOI: 10.1016/j.jep.2004.07.008

[24] U. Sirion, S. Kasemsook, K. Suksen, P. Piyachaturawat, A. Suksamrarn and R. Saeeng: New substituted C-19Andrographolide analogues with potent cytotoxic activities. Bioorg Med Chem Lett, 22(1), 49-52 (2012) DOI: 10.1016/j.bmcl.2011.11.085

[25] M. L. Tan, H. K. Tan, C. E. Oon, M. Kuroyanagi and T. S. Muhammad: Identification of genes involved in the regulation of 14-deoxy-11,12didehydroAndrographolide-induced toxicity in T-47D mammary cells. Food Chem Toxicol, 50(2), 431-44 (2012) DOI: 10.1016/j.fct.2011.11.001

[26] A. D. Thingale, K. S. Shaikh, P. R. Channekar, U. C. Galgatte, P. D. Chaudhari and C. Bothiraja: Enhanced hepatoprotective activity of Andrographolide complexed with a biomaterial. Drug Deliv, (2014) DOI: 10.3109/10717544.2013.871602

[27] S. S. Handa and A. Sharma: Hepatoprotective activity of Andrographolide from Andrographis paniculata against carbontetrachloride. Ind J Med Res, 92, 276-83 (1990)

[28] C. Tang, G. Gu, B. Wang, X. Deng, X. Zhu, H. Qian and W. Huang: Design, synthesis, and biological evaluation of Andrographolide derivatives as potent hepatoprotective agents. Chem Biol Drug Des, 83(3), 324-33 (2014) DOI: 10.1111/cbdd.12246

[29] N. P. Trivedi, U. M. Rawal and B. P. PaTel: Potency of Andrographolide as an antitumor compound in BHC-induced liver damage. Integr Cancer Ther, 8(2), 177-89 (2009) DOI: 10.1177/1534735409335606

[30] P. K. Visen, B. Saraswat, V. Vuksan and B. Dhawan: Effect of Andrographolide on monkey hepatocytes against galactosamine induced cell toxicity: an in-vitro study. J Comp Integr Med, 4(1) (2007)

[31] P. K. Visen, B. Shukla, G. K. Patnaik and B. N. Dhawan: Andrographolide protects rat hepatocytes against paracetamolinduced damage. J Ethnopharmacol, 40(2), 131-6 (1993) DOI: 10.1016/0378-8741(93)90058-D

[32] Y. F. Xia, B. Q. Ye, Y. D. Li, J. G. Wang, X. J. He, X. Lin, X. Yao, D. Ma, A. Slungaard, R. P. Hebbel, N. S. Key and J. G. Geng: Andrographolide attenuates inflammation by inhibition of NF-kappa B activation through covalent modification of reduced cysteine 62 of p50. J Immunol, 173(6), 4207-17 (2004) DOI: 10.4049/jimmunol.173.6.4207

[33] Y. J. Wang, J. T. Wang, Q. X. Fan and J. G. Geng: Andrographolide inhibits NF-kappaBeta activation and attenuates neointimal hyperplasia in arterial restenosis. Cell Res, 17(11), 933-41 (2007) DOI: 10.1038/cr.2007.89

[34] N. Mackman: Regulation of the tissue factor gene. ThrombsHaemo, 78(1), 747-54 (1997)

[35] Y. D. Li, B. Q. Ye, S. X. Zheng, J. T. Wang, J. G. Wang, M. Chen, J. G. Liu, X. H. Pei, L. J. Wang, Z. X. Lin, K. Gupta, N. Mackman, A. Slungaard, N. S. Key and J. G. Geng: NF-kappaB transcription factor p50 critically regulates tissue factor in deep vein thrombosis. J Biol Chem, 284(7), 4473-83 (2009) DOI: 10.1074/jbc.M806010200

[36] L. Huang: The effects of Andrographolides on experimental blood deficiency of cardiac muscle. Chin Herb Med, 18(7), 26-28 (1987)

[37] H. W. Chen, A. H. Lin, H. C. Chu, C. C. Li, C. W. Tsai, C. Y. Chao, C. J. Wang, C. K. Lii and K. L. Liu: Inhibition of TNF-alphaInduced Inflammation by Andrographolide via down-regulation of the PI3K/Akt signaling pathway. J

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Nat Prod, 74(11), 2408-13 (2011) DOI: 10.1021/np200631v

[38] H. R. Tsai, L. M. Yang, W. J. Tsai and W. F. Chiou: Andrographolide acts through inhibition of ERK1/2 and Akt phosphorylation to suppress chemotactic migration. Eur J Pharmacol, 498(1-3), 45-52 (2004) DOI: 10.1016/j.ejphar.2004.07.077

[39] L. J. Wang, X. Zhou, W. Wang, F. Tang, C. L. Qi, X. Yang, S. Wu, Y. Q. Lin, J. T. Wang and J. G. Geng: Andrographolide inhibits oral squamous cell carcinogenesis through NF-kappaB inactivation. J Dent Res, 90(10), 1246-52 (2011) DOI: 10.1177/0022034511418341

[40] K. C. Lee, H. H. Chang, Y. H. Chung and T. Y. Lee: Andrographolide acts as an antiinflammatory agent in LPS-stimulated RAW264.7. macrophages by inhibiting STAT3-mediated suppression of the NF-kappaB pathway. J Ethnopharmacol, 135(3), 678-84 (2011) DOI: 10.1016/j.jep.2011.03.068

[41] V. Chandrasekaran, P. Thiyagarajan, H. B. Deepak and A. Agarwal: In vitro modulation of LPS/calcimycin induced inflammatory and allergic mediators by pure compounds of Andrographis paniculata (King of bitters) extract. IntImmunopharmacol, 11(1), 79-84 (2011) DOI: 10.1016/j.intimp.2010.10.009

[42] Y. Chao, C. K. Lii, I. T. Tsai, C. C. Li, K. L. Liu, C. W. Tsai and H. W. Chen: Andrographolide inhibits ICAM-1 expression and NF-kappaB activation in TNF-alpha-treated EA.hy926 cells. J Agric Food Chem, 59(10), 5263-71 (2011) DOI: 10.1021/jf104003y

[43] W. Chen, L. Feng, H. Nie and X. Zheng: Andrographolide induces autophagic cell death in human liver cancer cells through cyclophilin D-mediated mitochondrial permeability transition pore. Carcinogenesis, 33(11), 2190-8 (2012) DOI: 10.1093/carcin/bgs264

[44] Y. C. Shen, C. F. Chen and W. F. Chiou: Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism(s) involved in its anti-inflammatory effect. Br J Pharmacol, 135(2), 399-406 (2002) DOI: 10.1038/sj.bjp.0704493

[45] W. F. Chiou, C. F. Chen and J. J. Lin: Mechanisms of suppression of inducible nitric oxide synthase (iNOS) expression in RAW 264.7. cells by Andrographolide. Br J Pharmacol, 129(8), 1553-60 (2000) DOI: 10.1038/sj.bjp.0703191

[46] L. Ying and L. J. Hofseth: An emerging role for endothelial nitric oxide synthase in chronic inflammation and cancer. CanRes, 67(4), 1407-10 (2007) DOI: 10.1158/0008-5472.CAN-06-2149

[47] Hanahan and R. A. Weinberg: Hallmarks of cancer: the next generation. Cell, 144(5), 646-74 (2011) DOI: 10.1016/j.cell.2011.02.013

[48] D. J. Newman and G. M. Cragg: Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod, 75(3), 311-35 (2012) DOI: 10.1021/np200906s

[49] B. B. Zhou, H. Zhang, M. Damelin, K. G. Geles, J. C. Grindley and P. B. Dirks: Tumour-initiating cells: challenges and opportunities for anticancer drug discovery. Nat Rev Drug Discov, 8(10), 806-23 (2009) DOI: 10.1038/nrd2137

[50] Y. A. Kim, M. Y. Kim, H. Y. Yu, S. K. Mishra, J. H. Lee, K. S. Choi, J. H. Kim, Y. K. Xiang and Y. S. Jung: Gadd45beta is transcriptionally activated by p53 via p38alpha-mediated phosphorylation during myocardial ischemic injury. J Mol Med (Berl), 91(11), 1303-13 (2013) DOI: 10.1007/s00109-013-1070-9

[51] S. K. Mishra, J. H. Kang, D. K. Kim, S. H. Oh and M. K. Kim: Orally administered aqueous extract of Inonotus obliquus ameliorates acute inflammation in dextran sulfate sodium (DSS)-induced colitis in mice. J Ethnopharmacol, 143(2), 524-32 (2012) DOI: 10.1016/j.jep.2012.07.008

[52] S. K. Mishra, J. H. Kang, C. W. Lee, S. H. Oh, J. S. Ryu, Y. S. Bae and H. M. Kim: Midazolam induces cellular apoptosis in human cancer cells and inhibits tumor growth in xenograft mice.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Mol Cells, 36(3), 219-26 (2013) DOI: 10.1007/s10059-013-0050-9

[53] S. K. Mishra, J.-H. Kang, K.-H. Song, M. S. Park, D.-K. Kim, Y.-J. Park, C. Choi, H. M. Kim, M. K. Kim and S. H. Oh: Inonotus obliquus suppresses proliferation of colorectal cancer cells and tumor growth in mice models by downregulation of β-catenin/NF-κB-signaling pathways. Eur J Inflamm, 11(3), 615-629 (2013)

[54] R. A. Kumar, K. Sridevi, N. V. Kumar, S. Nanduri and S. Rajagopal: Anticancer and immunostimulatory compounds from Andrographis paniculata. J Ethnopharmacol, 92(2-3), 291-5 (2004) DOI: 10.1016/j.jep.2004.03.004

[55] S. Nanduri, V. K. Nyavanandi, S. S. Thunuguntla, S. Kasu, M. K. Pallerla, P. S. Ram, S. Rajagopal, R. A. Kumar, R. Ramanujam, J. M. Babu, K. Vyas, A. S. Devi, G. O. Reddy and V. Akella: Synthesis and structure-activity relationships of Andrographolide analogues as novel cytotoxic agents. Bioorg Med Chem Lett, 14(18), 4711-7 (2004) DOI: 10.1016/j.bmcl.2004.06.090

[56] H. P. Chao, C. D. Kuo, J. H. Chiu and S. L. Fu: Andrographolide exhibits anti-invasive activity against colon cancer cells via inhibition of MMP2 activity. Planta Med, 76(16), 1827-33 (2010) DOI: 10.1055/s-0030-1250039

[57] Y. H. Lai, S. L. Yu, H. Y. Chen, C. C. Wang, H. W. Chen and J. J. Chen: The HLJ1-targeting drug screening identified Chinese herb Andrographolide that can suppress tumourgrowth and invasion in non-small-cell lung cancer. Carcinogenesis, 34(5), 1069-80 (2013) DOI: 10.1093/carcin/bgt005

[58] P. Pratheeshkumar and G. Kuttan: Andrographolide inhibits human umbilical vein endothelial cell invasion and migration by regulating MMP-2 and MMP-9 during angiogenesis. J Environ PatholToxicol Oncol, 30(1), 33-41 (2011) DOI: 10.1615/JEnvironPatholToxicolOncol.v30.i1.40

[59] S. H. Liu, C. H. Lin, F. P. Liang, P. F. Chen, C. D. Kuo, M. M. Alam, B. Maiti, S. K. Hung, C. W. Chi, C. M. Sun and S. L. Fu: Andrographolide downregulates the v-Src and Bcr-Abl oncoproteins and induces Hsp90 cleavage in the ROS-dependent suppression of cancer malignancy. BiochemPharmacol, 87(2), 229-42 (2014) DOI: 10.1016/j.bcp.2013.10.014

[60] A. Jaruchotikamol, K. Jarukamjorn, W. Sirisangtrakul, T. Sakuma, Y. Kawasaki and N. Nemoto: Strong synergistic induction of CYP1A1 expression by Andrographolide plus typical CYP1A inducers in mouse hepatocytes. Toxicol App Pharmacol, 224(2), 156-62 (2007) DOI: 10.1016/j.taap.2007.07.008

[61] J. Li, H. Y. Cheung, Z. Zhang, G. K. Chan and W. F. Fong: Andrographolide induces cell cycle arrest at G2/M phase and cell death in HepG2 cells via alteration of reactive oxygen species. Eur J Pharmacol, 568(1-3), 31-44 (2007) DOI: 10.1016/j.ejphar.2007.04.027

[62] K. K. Shen, T. Y. Liu, C. Xu, L. L. Ji and Z. T. Wang: Andrographolide inhibits hepatoma cells growth and affects the expression of cell cycle related proteins. Acta Pharma Sinica, 44(9), 973-9 (2009)

[63] J. Zhou, S. E. Hu, S. H. Tan, R. Cao, Y. Chen, D. Xia, X. Zhu, X. F. Yang, C. N. Ong and H. M. Shen: Andrographolide sensitizes cisplatin-induced apoptosis via suppression of autophagosomelysosome fusion in human cancer cells. Autophagy, 8(3), 338-49 (2012) DOI: 10.4161/auto.18721

[64] Y. Y. Zhu, G. Yu, Y. Zhang, Z. Xu, Y. Q. Wang, G. R. Yan and Q. Y. He: A novel Andrographolide derivative AL-1 exerts its cytotoxicity on K562 cells through a ROSdependent mechanism. Proteomics, 13(1), 169-78 (2013) DOI: 10.1002/pmic.201200273

[65] Y. Li, P. Zhang, F. Qiu, L. Chen, C. Miao, J. Li, W. Xiao and E. Ma: Inactivation of PI3K/Akt signaling mediates proliferation inhibition and G2/M phase arrest induced by Andrographolide in human glioblastoma cells. Life Sci, 90(25-26), 962-7 (2012) DOI: 10.1016/j.lfs.2012.04.044

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[66] T. Suriyo, N. Pholphana, N. Rangkadilok, A. Thiantanawat, P. Watcharasit and J. Satayavivad: Andrographis paniculata Extracts and Major Constituent

[67] Diterpenoids Inhibit Growth of Intrahepatic Cholangiocarcinoma Cells by Inducing Cell Cycle Arrest and Apoptosis. Planta Med, 80(7), 533-543 (2014) DOI: 10.1055/s-0034-1368399

[68] D. Chen, Y. Song, Y. Lu and X. Xue: Synthesis and in vitro cytotoxicity of Andrographolide-19-oic acid analogues as anti-cancer agents. Bioorg Med Chem Lett, 23(11), 3166-9 (2013) DOI: 10.1016/j.bmcl.2013.04.010

[69] S. H. Kaufmann and W. C. Earnshaw: Induction of apoptosis by cancer chemotherapy. Exp Cell Res, 256(1), 42-9 (2000) DOI: 10.1006/excr.2000.4838S. Sukumari-Ramesh, J. N. Bentley, M.

[70] D. Laird, N. Singh, J. R. Vender and K. M. Dhandapani: Dietary phytochemicals induce p53- and caspase-independent cell death in human neuroblastoma cells. Int J Dev Neurosci, 29(7), 701-10 (2011) DOI: 10.1016/j.ijdevneu.2011.06.002

[71] Y. Wu and B. P. Zhou: Inflammation: a driving force speeds cancer metastasis. Cell Cycle, 8(20), 3267-73 (2009) DOI: 10.4161/cc.8.20.9699

[72] L. Yang, D. Wu, K. Luo, S. Wu and P. Wu: Andrographolide enhances 5-fluorouracil-induced apoptosis via caspase-8-dependent mitochondrial pathway involving p53 participation in hepatocellular carcinoma (SMMC-7721) cells. Can Lett, 276(2), 180-188 (2009) DOI: 10.1016/j.canlet.2008.11.015

[73] J. Zhou, G. D. Lu, C. S. Ong, C. N. Ong and H. M. Shen: Andrographolide sensitizes cancer cells to TRAIL-induced apoptosis via p53-mediated death receptor 4 up-regulation. Mol Can Ther, 7(7), 2170-80 (2008) DOI: 10.1158/1535-7163.MCT-08-0071

[74] Y. Tan, K. H. Chiow, D. Huang and S. H. Wong: Andrographolide regulates epidermal growth factor receptor and transferrin receptor trafficking in epidermoid carcinoma (A-431) cells. Br J Pharmacol, 159(7), 1497-510 (2010) DOI: 10.1111/j.1476-5381.2009.00627.x

[75] J. Y. Chun, R. Tummala, N. Nadiminty, W. Lou, C. Liu, J. Yang, C. P. Evans, Q. Zhou and A. C. Gao: Andrographolide, an herbal medicine, inhibits interleukin-6 expression and suppresses prostate cancer cell growth. Genes Can, 1(8), 86876 (2010) DOI: 10.1177/1947601910383416

[76] J. Nateewattana, R. Saeeng, S. Kasemsook, K. Suksen, S. Dutta, S. Jariyawat, A. Chairoungdua, A. Suksamrarn and P. Piyachaturawat: Inhibition of topoisomerase II alpha activity and induction of apoptosis in mammalian cells by semi-synthetic Andrographolide analogues. Invest New Drugs, 31(2), 32032 (2013) DOI: 10.1007/s10637-012-9868-9

[77] S. Kumar, H. S. Patil, P. Sharma, D. Kumar, S. Dasari, V. G. Puranik, H. V. Thulasiram and G. C. Kundu: Andrographolide inhibits osteopontin expression and breast tumor growth through down regulation of PI3 kinase/Akt signaling pathway. Curr Mol Med, 12(8), 952-66 (2012) DOI: 10.2174/156652412802480826

[78] M. D. Shi, H. H. Lin, Y. C. Lee, J. K. Chao, R. A. Lin and J. H. Chen: Inhibition of cellcycle progression in human colorectal carcinoma Lovo cells by Andrographolide. Chem-Bio Inter, 174(3), 201-10 (2008) DOI: 10.1016/j.cbi.2008.06.006

[79] J. Nateewattana, S. Dutta, S. Reabroi, R. Saeeng, S. Kasemsook, A. Chairoungdua, J. Weerachayaphorn, S. Wongkhamand P. Piyachaturawat: Induction of apoptosis in cholangiocarcinoma by an Andrographolide analogue is mediated through topoisomerase II alpha inhibition. Eur J Pharmacol, 723, 148-55 (2014) DOI: 10.1016/j.ejphar.2013.12.002

[80] P. Roy, S. Das, A. Mondal, U. Chatterji and A. Mukherjee: Nanoparticle engineering enhances anticancer efficacy of Andrographolide in MCF-7 cells and mice bearing EAC. Curr Pharma Biotech, 13(15), 2669-81 (2012) DOI: 10.2174/138920112804724855

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CODEN: JCLMC4
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[81] H. H. Lin, C. W. Tsai, F. P. Chou, C. J. Wang, S. W. Hsuan, C. K. Wang and J. H. Chen: Andrographolide down-regulates hypoxia-inducible factor-1alpha in human non-small cell lung cancer A549 cells. Toxicol Appl Pharmacol, 250(3), 336-45 (2011) DOI: 10.1016/j.taap.2010.11.014

[82] K. Sheeja and G. Kuttan: Protective effect of Andrographis paniculata and Andrographolide on cyclophosphamideinduced urothelial toxicity. Integr Can Ther, 5(3), 244-51 (2006) DOI: 10.1177/1534735406291984

[83] H. J. Hocker, K. J. Cho, C. Y. Chen, N. Rambahal, S. R. Sagineedu, K. Shaari, J. Stanslas, J. F. Hancock and A. A. Gorfe: Andrographolide derivatives inhibit guanine nucleotide exchange and abrogate oncogenic Ras function. Proc Natl Acad Sci U S A, 110(25), 10201-6 (2013) DOI: 10.1073/pnas.1300016110

[84] S. Kasemsuk, U. Sirion, K. Suksen, P. Piyachaturawat, A. Suksamrarn and R. Saeeng: 12-Amino-Andrographolide analogues: synthesis and cytotoxic activity. ArchPharmaRes, 36(12), 145464 (2013) DOI: 10.1007/s12272-013-0152-0