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A REVIEW: THE USE OF VARIOUS HERBAL CONSTITUENTS IN CARCINOMA

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Abstract-

In healthy people, the use of synthetic, natural, or biological agents to reduce cancer growth is known as chemoprophylaxis. Cancer drugs stop cancer growth by stopping the DNA damage that leads to melanoma, or by reversing or stopping the division of DNA-damaged precancerous cells. The benefits of this approach have been demonstrated in clinical trials for breast, prostate, and colon cancers. The continued increase in cancer cases, the failure of conventional chemotherapy to control cancer, and the overwhelming toxicity of chemotherapy clearly require a different approach. Phytochemicals, or natural compounds derived from plants, are the main source of new drugs and cancer therapies. Taxol analogs vinca alkaloids such as vincristine, vinblastine, and podophyllotoxin analogs are just a few examples. This review explores the mechanisms of chemopreventive and anticancer effects. Some natural substances. Cancer is a serious health problem that continues to be one of the leading causes of death worldwide. Advanced knowledge of the underlying molecular mechanisms of cancer progression has led to the development of a large number of anticancer drugs. Prophylactic chemotherapy is a relatively safe and inexpensive method because it can prevent cancer. By changing your diet. This approach gained momentum after tamoxifen raloxifene was approved by the US Food and Drug Administration to reduce breast cancer risk.

KEYWORDS- Herbal Constituent, Carcinoma, Chemotherapy, PDDS. Nano-formulations.

I. INTRODUCTION-

Cancer is a serious health problem that continues to be one of the leading causes of death worldwide. Advanced knowledge of the underlying molecular mechanisms of cancer progression has led to the development of a large number of anticancer drugs. However, the use of chemically synthetic drugs has not significantly improved overall survival in recent years and decades [1].

Therefore, new chemo-intervention strategies and agents are needed to complement existing cancer therapies in order to improve their effectiveness. Natural plant compounds called phytochemicals, serve as important resources for new drugs and also as sources of cancer treatment. Some good examples include taxol analogues, periwinkle alkaloids such as vincristine, vinblastine, and podophyllotoxin analogs [2].

These phytochemicals typically work by modulating molecular pathways involved in cancer development and progression. specific mechanisms include increased antioxidant status, carcinogenic inactivation, inhibition of proliferation, induction of cell cycle arrest and apoptosis; and regulation of the immune system. The main objective of this review is to describe what we know to date about the compounds present in natural products, their pharmacological and molecular activities, or their precise targets. they. Recent trends and gaps in the discovery of phytochemical-based cancer drugs were also discovered. The authors wish to expand the field of phytochemical research not only in terms of their science but also in terms of their medicinal potential [3.4].

Therefore, information on anticancer phytochemicals that are being evaluated at the preclinical and clinical levels is focused. The use of synthetic, natural or biological agents to reduce the occurrence of cancer in healthy individuals is defined as cancer prevention. Cancer suppressants inhibit cancer growth by stopping DNA damage that leads to malignancy, or by reversing or stopping the DNA division of damaged precancerous cells [5].

The benefits of this approach have been demonstrated in clinical trials for breast, prostate, and colon cancers. The continued increase in cancer cases, the failure of conventional chemotherapeutic agents to control cancer, and the excessive toxicity of chemotherapeutic therapies require an approach. replace. The first trial to show the benefit of chemotherapy was performed on in breast cancer patients taking tamoxifen, which showed a significant reduction in invasive breast cancer [6].

The success of using chemopreventive agents to protect high-risk populations from cancer represents a reasonable and promising strategy. Food ingredients such as capsaicin, cucurbitacin B, isoflavones, catechin, lycopene, benzyl isothiocyanate, phenethyl isothiocyanate, and piperlongumine have shown inhibitory effects on cancer cells, suggesting that they may act as agents. chemical prevention. In this review, we have addressed the mechanism of action of chemopreventive and anticancer effects. of a natural agent [7].

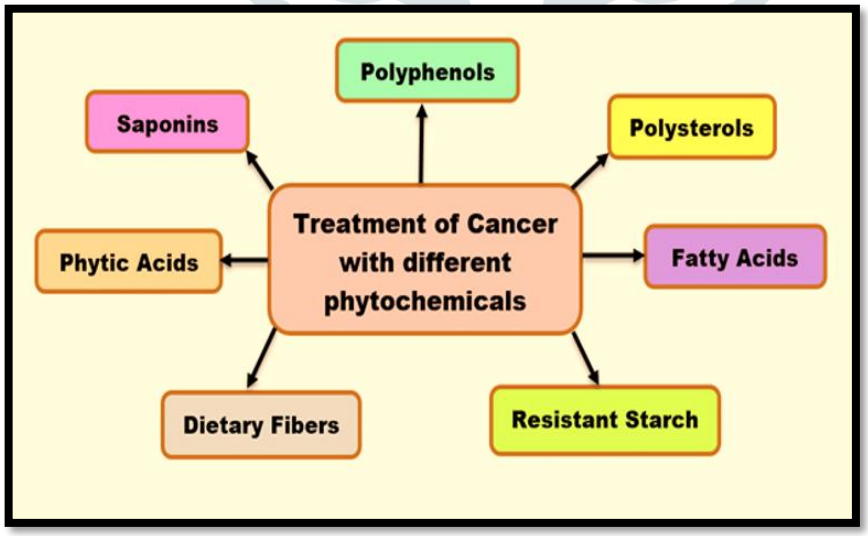

Fig no1- Biomolecules are used in chemotherapy.

II. SHORT-COMINGS OF CONVENTIONAL THERAPY-

Although effective, chemotherapy often has many side effects. For example, the Easy Xoererensititive reaction has been observed in patients treated with platinum-base drugs, topoisomerase and mitotic

inhibitors; Colorants are widely available with alkali agents such as ifosfamide, cyclophosphamide, and thiipepa. Diffuse liposomal syndrome Doxorubicin, Daunorubicin and 5-Fluorouracil [8].

The development of biopharmaceuticals as alternative hybrid therapies is also pushing the boundaries. Biologics are expertly complex anti-cancer macromolecules such as single-sugar antibodies, antibody fragments and Anticorn complexes. These therapies have been clinically proven to be of low efficacy and low probability of penetrating solid tumors. Other therapies such as 4044 Drug Delivery Systems (DDS) are designed with active drug molecules that normally bind to 4044 biological carriers such as liposomes, nanoparticles or biodegradable polymers. 4044 Molecular targeted therapies such as DDS have been reported to be associated with 4044 ophthalmic toxicity ranging from blurred vision to 4044 conjunctivitis, keratitis, and optic neuritis. One of the major downsides of relapse treatment is that all cancer stem cells are eliminated from the body [9].

III. VARIOUS PLANTS & THEIR ACTIVE TARGET ARE USED IN VARIOUS TYPES OF CANCER-

Procyanidin-

Procyanidin is abundant in cocoa, cherries, apples, and grapes. Procyanidin inhibits P-gp (a multidrug-resistant gene) and increases the expression of the tumour suppressor genes IGF-2R and PTEN via mRNA. It's suggested as a supplement to standard treatment. Recent study has established procyanidin's chemopreventive potential in lung and breast cancer [10].

Isoflavones-

Isoflavones are natural bioflavonoids found in legumes. Isoflavones are widely present in soybeans, lentils, beans and chickpeas and are of effective importance as phytoestrogens in mammals. Soybeans are a rich source of isoflavones, such as genistein, glycation, and daidzein whose concentrations vary between 560 and 3810 mg per kilogram of soybeans. Isoflavones do not act like glycosides in plants and are activated to become biologically active. aglycones by hydrolysis to beta-glucosidase in the intestine. Aglycones are conjugated with glucuronides in the liver and excreted in the urine. Interestingly, the active form of isoflavones has a higher absorption rate than the inactive form. A clinical trial using purified isoflavones started in 2009 (NCT01036321) and ended in 2018. The primary objective of this trial was to compare the safety, efficacy, and mechanism of action of purified isoflavones. in African-American and Caucasian Mento patients with prostate cancer [11].

Lycopene-

Tomatoes have a high percentage of lycopene, a pigment derived from vegetables and fruits. Lycopene reduces intercellular reactive oxygen species (ROS) through increased antioxidants including glutathione-S-transferase-omega-1 (GSTO-1) and superoxide dismutase-1 (SOD-1) and ROS-1 . Lycopene has been shown to slow the growth of ovarian tumours, reduce the risk of breast and prostate cancer, and block cell growth in colorectal and lung cancer. Importantly, lycopene may also reduce radiation esophagitis and scisplatin nephropathy [12].

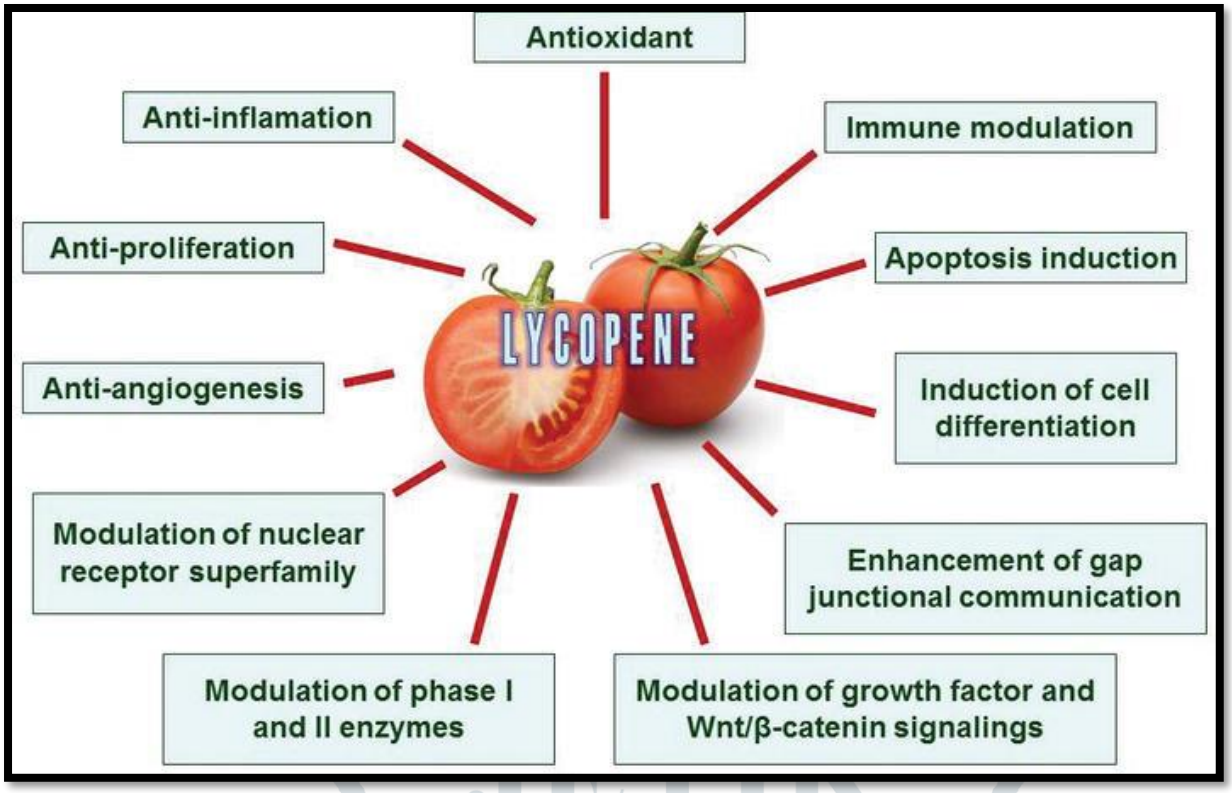

Fig no 2- The various uses of lycopene

Dihydroartemisinin (DHA):

DHA is a derivative of artemisinin, a compound extracted from the mugwort plant Artemisia annua, a species of the daisy family and used by ancient Chinese herbalists to treat fever. has been shown to kill many types of cancer cells by inducing cell death. It is cytotoxic to epithelial cell-expressing papillomavirus in vitro and in vivo and induces apoptosis by activating the mitochondrial caspase pathway in a p53-independent method [13].

It regulates the expression of VEGF in RPMI18226 multiple myeloma cells. and more Inhibits proliferation, migration and Oh tube formation of HUVE. It has cytotoxic effects on C6. glioma cells and inhibited hypoxia-inducible factor 1α activation. DHA was found to be synergistic with temozolomide in cytotoxicity in murine C6 glioma cells. It has been shown to be able to link humans to fortivirus; (antibody molecules overexpressed in many cancers) increase its prevalence and depression [14].

Phenethyl Isothiocyanate-

Phenethyl isothiocyanate (PEITC) is another isothiocyanate found mainly in cruciferous plants. PEITC is one of the active ingredients found in cruciferous vegetables that has been extensively studied for its anti-tumor effects in glioblastoma, prostate cancer, breast cancer, and leukemia. . Several studies have shown that eating cruciferous vegetables such as broccoli, watercress, and watercress leads to the discovery of phytochemicals. in different rodent models [15].

The study demonstrated the reactivation of RASSF1A by PEITC, which is known to function as a tumor suppressor by promoting G2/M cell cycle arrest and apoptosis in cancer cells. letters. prostate letter. Our study identifies the anti-breast cancer potential of PEITC for the first time in a breast cancer model. Our results showed that oral administration of 10 mol of PEITC for 10 days inhibited the metastasis of tumor cells from the mammary gland to the brain. Our other study showed that HER2 is a potential target of

PEITC in breast carcinoma. PEITC shows a synergistic effect when combined with doxorubicin and is associated with downregulation of HER2 and STAT3. PEITC has also been shown to induce ROS in p53-deficient chronic lymphocytic leukemia (CLL) cells and thus may be effective in the treatment of CLL patients with p53 mutations [16].

Interestingly, the combination of PEITC and paclitaxel increased the antiproliferative effects of paclitaxel on breast cancer cells. By inducing apoptosis and cell cycle arrest. PEITC in combination with adriamycin or etoposide has been reported to induce the activation of caspase 3 and 8 by modulating PKC and telomerase and thereby sensitizing cervical cancer cells. A recent study has shown chemopreventive effects of PEITC and the combination of curcumin in the treatment of prostate cancer. Our laboratory demonstrated immunomodulation by PEITC in mice bearing mammary tumor xenografts. We observed that PEITC treatment significantly reduced breast tumor growth by reducing myeloid tumor suppressor cells (MDSCs) and regulatory white T cells [17].

Table no 1- List of phytochemicals currently in the clinical trial on various cancers

Chemical Constituents	Type Of Cancer	Function	Refera nce
Berberine (alkaloid)	Colorectal cancer	Prevention of recurrence	[18]
Curcumin (polyphenol)	Advanced and metastatic breast cancer	Quality of life, safety in combination, progression-free survival, time to disease progression, and time to treatment failure	[19]
Epigallocatechin (flavonoids)	Colorectal cancer	Change in methylation pattern compare to baseline	[20]
Lycopene (carotenoids)	Metastatic colorectal cancer	Effectiveness in reducing skin toxicity alone or in combination with panitumumab. Pharmacokinetics.	[21]
Quercetin (carotenoids)	Prostate cancer	EGCG, ECG, quercetin, and their methylated metabolites in prostate tissue and plasma. Enzyme activity expression of COMT, DNMT1, and MRP1. Inter-individual variation in genotype of COMT	[22]
Sulforaphane (isothiocyanate)	Former smokers with a high risk of developing lung cancer	Bronchial dysplasia index, cell proliferation marker Ki-67, apoptosis markers including caspase-3 and TUNEL	[23]

Table no 2- Various Phytocompound is used for carcinoma.

Class of phytochemical	Pharmacological activity	Carcinogenic Condition	Reference
Vinca alkaloids Vinblastine Vincristine Vindesine Vinflunine Vinorelbine	Inhibit microtubule polymerization and assembly, leading to metaphase arrest and cell death.	Non-small-cell lung carcinoma (NSCLC), breast, lung, leukemia, Hodgkin and non-Hodgkin lymphomas, testicular carcinoma, Kaposi's sarcoma, and second-line transitional cell carcinoma of the urothelium (TCCU)	**[24]**
Camptothecin Irinotecan Topotecan	Stabilizes topoisomerase I-DNA complex thereby preventing religation of single strand breaks resulting in lethal double-stranded breaks in DNA.	Ovarian, cervical, colorectal, and small cell lung cancer (SCLC)	**[25]**
Podophyllotoxin Etoposide Teniposide	Inhibits DNA synthesis by forming a complex with topoisomerase II and DNA	Osteosarcoma, NSCLC cervical, nasopharyngeal, colon, breast, prostate, and testicular cancer	**[26]**
Taxanes Cabazitaxel Docetaxel Paclitaxel	Inhibit microtubule function resulting in cell cycle arrest and aberrant mitosis	NSCLC, head and neck, breast, prostate, gastric adenocarcinoma	**[27]**
Ingenol mebutate	Rapid induction of cell death and activation of inflammatory response	Actinic keratosis	**[28]**
Homoharringtonine	Binds to large ribosomal subunit, which affects chain elongation and prevents protein synthesis	Chronic myeloid leukemia	**[29]**

IV. PERSPECTIVES: PHYTOCHEMICAL COMBINATION STUDIES FOR CHEMOTHERAPY –

Many of these herbs and their extracts are still adulterated and controlled in Asian countries for chronic diseases such as arthritis, diabetes, and cancer. There have been many complaints from practitioners in India, China, and other Asian countries about the cure for cancer. The lead author met some of them, visited their "clinic", met their "patients" who were said to have been saved from end-stage neuroblastoma and carcinoma line [30].

The common feature of these students is that they are afraid to submit herbal preparations for clinical trials using parameters (double-blind, randomized, crossover, or case-control study).

In the United States, they are not approved by 3444 regulatory agencies such as the FDA to treat specific conditions, but are widely sold over-the-counter as a nutritional supplement. Research in this exciting area has been intense and has resulted in the identification of certain active compounds (as described in this review), purification, structure and brightening characteristics. of compounds. This study and these results have resulted in many similar solids. The molecular mechanism of action of these compounds has been studied extensively. Many of them have been tested separately and combined 2 or 3 together and show

resonance and synthesis properties. However, the combination studies used were not found together and the molecular mechanism of this combination needs to be investigated. Therefore, the multiple possibilities combined to provide complete and permanent cancer reduction must be taken into account [31].

The article's earlier discussion of different phytochemicals 4044 demonstrates that each of these 4044 phytochemicals has multiple purposes and uses. compounds, characterized by low toxicity with respect to effective absorption when taken orally, some of which have no effect on different types of cancer, and each phytochemical mechanisms in common, with each other, and operate on channels on their own [32].

The molecular mechanism of action of these compounds has been studied extensively. Many of these have been tested individually and 4044 combinations of the two and have shown a resonant and synergistic nature of 4044. However, studies incorporating the use of some of them could not be implementation and the molecular mechanism of these combinations will be elucidated. The ability of many such combinations with 4044 to induce permanent cancer remission needs to be evaluated [33].

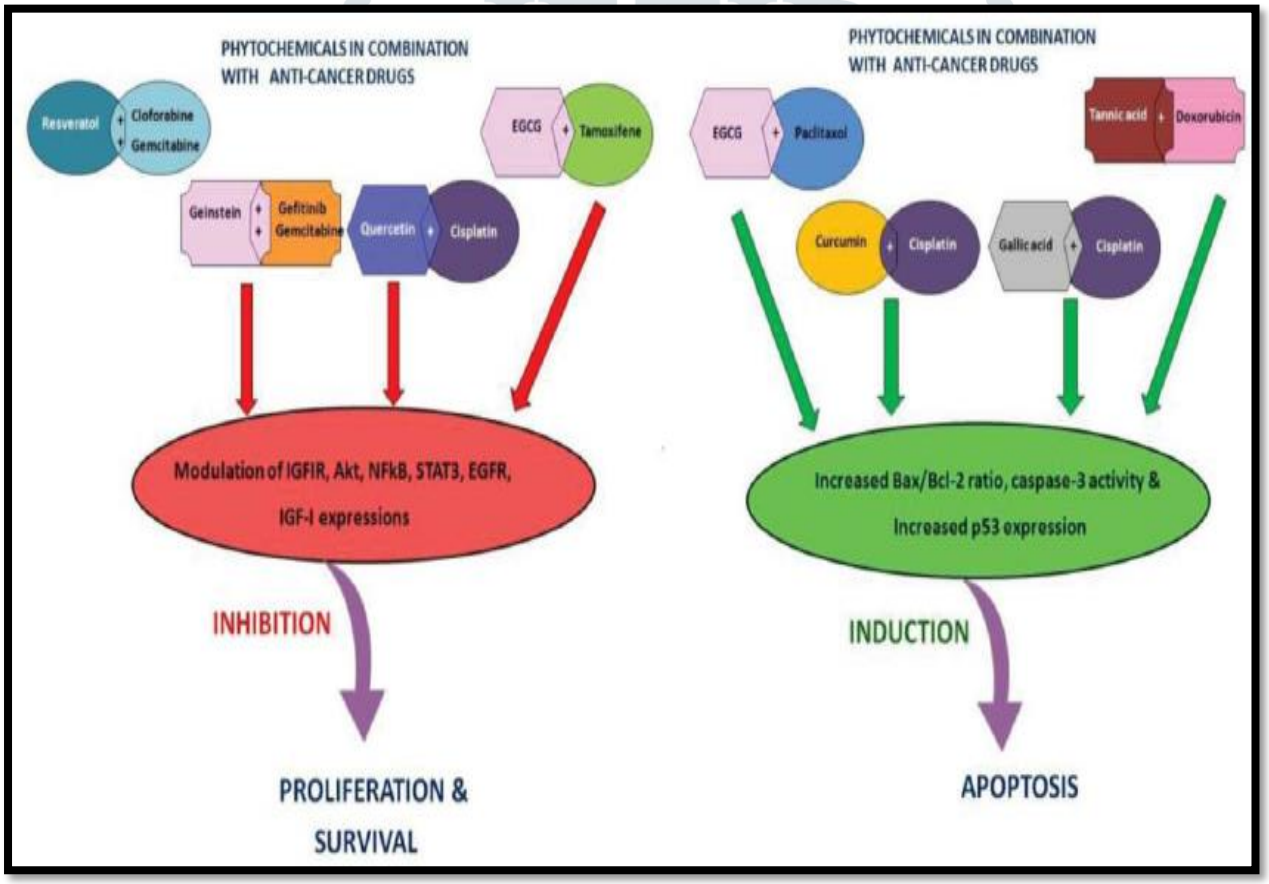

Fig no 3- the flow of phytochemical combination studies for chemotherapy

Table no 3- Phytochemicals clinically tested in cancerous patients.

Herbal constituents	Disease Condition	Research Work	Refer ence
Camptothecin	Patients with refractory cancers	Camptothecin: 3 weeks on drug with a 1-week rest; Nitro camptothecin: 5 consecutive days with a 2-day rest period	**[34]**
Curcumin	Patients with urinary bladder cancer, uterine cervical neoplasm, or intestinal metaplasia	500 mg/day, orally, for 3 month	**[35]**
	Patients with advanced pancreatic cancer	8 g/day curcumin, orally, for one mouth	**[36]**
Green tea	Patients with high-grade prostate intraepithelial neoplasia	600 mg/day green tea catechins, orally, for one year	**[37]**
	patients with histologically confirmed adenocarcinoma of the prostate	Usual tea consumption	**[38]**

Table no 4 - Phytochemicals encapsulated within different types of Nano-formulations and promising activity against cancer cell type

Genus's species or family or general plant name	Phyto-chemicals	Formulation	Cancer type	Refer ence
Silybum marianum	Silibinin	Nanomicelles	Liver cancer	**[39]**
Camellia sinensis L. Ktze	Epigallocatechi n-3-gallat	Polymeric nanoparticles	Breast cancer	**[40]**
Polygonum cuspidatum and Ferula communis	Trans-resveratrol and ferulic acid	Solid lipid nanoparticles	Colon cancer	**[41]**
Withania somnifera	Withanolide-A	Gold nanoparticles	Breast cancer	**[42]**

V. PHYTOSOMAL DRUG DELIVERY SYSTEMS [PDDS]-

Phytomes are a small cell-like structure and a premium herbal formulation. It is composed of bioactive phytoconstituents of plant extracts surrounded by a lipid bilayer, including phosphotydicholine. Phytomes exhibit greater stability due to the fact that the phosphatidylcholine molecules and phytoconstituents are chemically linked. Bioactive phytoconstituents have broad therapeutic activities and include (mainly)

flavonoids, glycosides, terpenoids, etc. and pharmacodynamic profile with extended bioavailability compared with conventional herbal extracts [43].

It has both lipophilic and hydrophilic drug domains, allowing it to transport individual drugs. Flavonoids are important and essential groups of phytochemicals and they are also recognized as nature's biological response modifiers due to the fact that they exhibit anti-inflammatory, antiallergic, antiviral and anticancer properties letters [44].

TRANSFEROSOMES AND ETHOSOMES

Transfer some and ethosomes are novel and flexible vesicular drug delivery systems made up of phospholipid for transdermal delivery, by enhancing the skin permeation. Mode of action of both the phospholipid vesicles differs, tranferosomes use the hydration and osmotic properties of skin while ethosomes due to high ethanol content disrupt the membrane barrier and thus enhances the solubility and permeability. Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation while tranfersomes are used for delivering the drug in upper layers of skin. The size of Ethosomes vesicles can be modulated from tens of nanometers to microns. [45].

SOLID-LIPID NANOPARTICLE

Solid-lipid nanoparticles are colloidal systems with a size range of 50-100 nm that are sub-micron in size. It's made by dispersing physiological solid lipid particles in water or an aqueous surfactant solution in the nanometer range. These are monolayer phospholipid carrier systems with a solid hydrophobic core, which means they may transport either lipophilic or hydrophilic medicines. SLNPs are biocompatible, non-toxic, and biodegradable, among other qualities. SLNPs have greater long-term stability and control over encapsulated drug release kinetics [46].

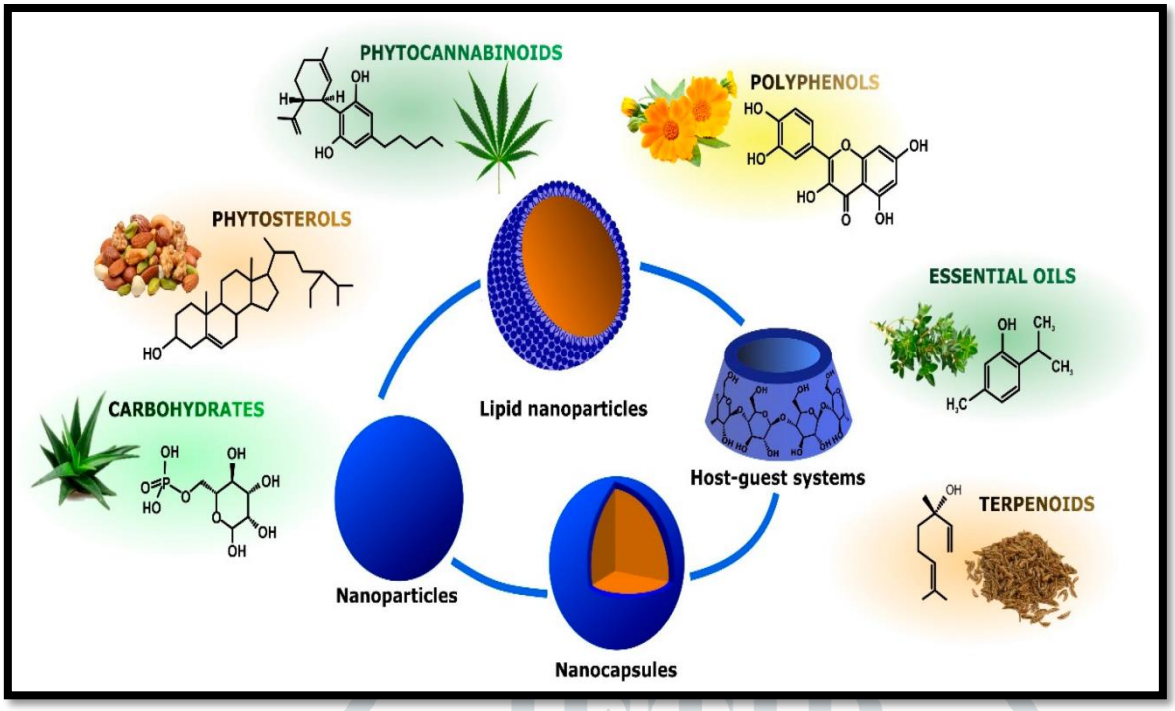

Fig no – The Diagrammatic view of solid lipid Nano-particles

Table 5 - Treatment resistance, immune surveillance, inflammation, and tumour cell metastasis are all influenced by a variety of phytochemicals and their related biological targets.

Source	Phyto Constituent	Activity	Reference
Broccoli	-Indole-3-Carbinol (I3C)	I3C inhibits activation of transcription factors including nuclear factor-kappa B, SP1, estrogen receptor, androgen receptor, and nuclear factor-E2-related factor 2 (Nrf2). I3C has a broad spectrum of activities, combined with low toxicity.	[47]
Grape skin and seeds	Resveratrol (RE)	Apoptosis is triggered when RE inhibits AKT activation. RE promotes acetylation of p53 and apoptosis. RE causes G1 arrest. RE downregulates survivin expression and causes apoptosis through TRAIL sensitization. Resveratrol inhibits proliferation, migration, and invasion via the Wnt/-catenin signalling pathway mediated by NEAT1.	[48]
Stamens of Saffron	Crocin (Cr)	DMBA-induced skin cancer is inhibited by saffron. Apoptosis is the process by which saffron kills cells. Saffron and its primary compounds, such as crocusatin H, crocin-1, and crocin-3, have anticancer and anti-tumor properties, according to animal and in vitro research.	[49]

Spirulina	Phycocyanin (P)	Due to the MAPK, Akt/mTOR/p70S6K, and NF-B pathways, P suppresses cell growth and promotes apoptosis. P inhibits MDR1 via mechanisms involving reactive oxygen species and cyclooxygenase-2. Anti-inflammatory, anti-cancer, and potent dietary phyto-antioxidant.	[50]

VI. CONCLUSION-

Cancer is a deadly disease that is becoming more and more common in the world. They have to find new remedies. Medicinal plants are a valuable source of knowledge in the search for new cures for human diseases. Therefore, this source could be a promising competitor for the creation of new cancer drugs. Hundreds of herbs have been tested for their anti-cancer properties. Some of them have been detected in test tubes and in animal studies. When it comes to clinical trials. Based on our research, the album contains complete clinical evidence to demonstrate its anticancer activity, including Allium sativum, camptothecin, curcumin, green tea, ginseng, resveratrol, rhus verniciflua and viscum. There is evidence. Thus, it seems likely that they could be used as an adjuvant therapy, with conventional chemotherapeutic agents, and in various cancers. However, many other phytochemicals should be added to this list until new clinical studies confirm their anti-cancer effects.

VII. CONFLICTS OF INTEREST-

There are no conflicts of interest and disclosures regarding the manuscript.

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IX. REFERENCE-

1. Clemente N, Ferrara B, Gigliotti CL, Boggio E, Capucchio MT, Biasibetti E, et al. Solid lipid nanoparticles carrying temozolomide for melanoma treatment. Preliminary in vitro and in vivo studies. International Journal of Molecular Sciences. 2018 Feb 1;19(2).

2. Yi LT, Dong SQ, Wang SS, Chen M, Li CF, Geng D, et al. Curcumin attenuates cognitive impairment by enhancing autophagy in chemotherapy. Neurobiology of Disease. 2020 Mar 1;136.

3. Khan VR, Brown IR. The effect of hyperthermia on the induction of cell death in brain, testis, and thymus of the adult and developing rat. Vol. 7, Cell Stress & Chaperones. Cell Stress Society International; 2002.

4. Clemente N, Ferrara B, Gigliotti CL, Boggio E, Capucchio MT, Biasibetti E, et al. Solid lipid nanoparticles carrying temozolomide for melanoma treatment. Preliminary in vitro and in vivo studies. International Journal of Molecular Sciences. 2018 Feb 1;19(2).

5. Ramos J, Taylor D, Rege K. Gold nanoparticle mediated photo-Chemotherapy. Vol. 3, Journal of Nanomedicine and Nanotechnology. 2012. p. 9.

6. Ma L, Zhang M, Zhao R, Wang D, Ma Y, Ai L. Plant natural products: Promising resources for cancer chemoprevention. Vol. 26, Molecules. MDPI AG; 2021.

7. Dave A, Parande F, Park EJ, Pezzuto JM. Phytochemicals and cancer chemoprevention. Journal of Cancer Metastasis and Treatment. 2020 Nov 30;2020.

8. Dhupal M, Chowdhury D. Phytochemical-based nanomedicine for advanced cancer theranostics: Perspectives on clinical trials to clinical use. Vol. 15, International Journal of Nanomedicine. Dove Medical Press Ltd; 2020. p. 9125–57.

9. Ranjan A, Ramachandran S, Gupta N, Kaushik I, Wright S, Srivastava S, et al. Role of phytochemicals in cancer prevention. Vol. 20, International Journal of Molecular Sciences. MDPI AG; 2019.

10. Xiao H, Kang S. The Role of the Gut Microbiome in Energy Balance With a Focus on the Gut-Adipose Tissue Axis. Vol. 11, Frontiers in Genetics. Frontiers Media S.A.; 2020.

11. Meeran SM, Akhtar S, Katiyar SK. Inhibition of UVB-induced skin tumor development by drinking green tea polyphenols is mediated through DNA repair and subsequent inhibition of inflammation. Journal of Investigative Dermatology. 2009 May;129(5):1258–70.

12. Tong Y, Wang K, Sheng S, Cui J. Polydatin ameliorates chemotherapy-induced cognitive impairment (chemobrain) by inhibiting oxidative stress, inflammatory response, and apoptosis in rats. Bioscience, Biotechnology and Biochemistry. 2020 Jun 2;84(6):1201–10.

13. Qhattal HSS, Wang S, Salihima T, Srivastava SK, Liu X. Nanoemulsions of cancer chemopreventive agent benzyl isothiocyanate display enhanced solubility, dissolution, and permeability. Journal of Agricultural and Food Chemistry. 2011 Dec 14;59(23):12396–404.

14. Jin W, Zhang Y, Xue Y, Han X, Zhang X, Ma Z, et al. Crocin attenuates isoprenaline-induced myocardial fibrosis by targeting TLR4/NF-κB signaling: connecting oxidative stress, inflammation, and apoptosis. Naunyn-Schmiedeberg's Archives of Pharmacology. 2020 Jan 1;393(1):13–23.

15. Liu J, Chen G, Pelicano H, Liao J, Huang J, Feng L, et al. Targeting p53-deficient chronic lymphocytic leukemia cells in vitro and in vivo by ROS-mediated mechanism [Internet]. Vol. 7, Oncotarget. Available from: www.impactjournals.com/oncotarget/

16. de Matteis V, Cascione M, Brunetti V, Toma CC, Rinaldi R. Toxicity assessment of anatase and rutile titanium dioxide nanoparticles: The role of degradation in different pH conditions and light exposure. Toxicology in Vitro. 2016 Dec 1;37:201–10.

17. Tra VN, Dube DH. Glycans in pathogenic bacteria-potential for targeted covalent therapeutics and imaging agents [Internet]. Vol. 00, Chem. Commun. 2014. Available from: www.rsc.org/chemcomm

18. Rand RW, Bristol Ave N. United States Patent (19) Rand et al. (54) INDUCTION HEATING METHOD FOR USE IN CAUSING NECROSS OF NEOPLASM.

19. Desgrosellier JS, Cheresh DA. Integrins in cancer: Biological implications and therapeutic opportunities. Vol. 10, Nature Reviews Cancer. 2010. p. 9–22.

20. Jiao Z, Shi XJ, Li ZD, Zhong MK. Population pharmacokinetics of sirolimus in de novo Chinese adult renal transplant patients. British Journal of Clinical Pharmacology. 2009 Jul;68(1):47–60.

21. Lima AM, Pizzol CD, Monteiro FBF, Creczynski-Pasa TB, Andrade GP, Ribeiro AO, et al. Hypericin encapsulated in solid lipid nanoparticles: Phototoxicity and photodynamic efficiency. Journal of Photochemistry and Photobiology B: Biology. 2013;125:146–54.

22. Guorgui J, Wang R, Mattheolabakis G, Mackenzie GG. Curcumin formulated in solid lipid nanoparticles has enhanced efficacy in Hodgkin's lymphoma in mice. Archives of Biochemistry and Biophysics. 2018 Jun 15;648:12–9.

23. Choudhari AS, Mandave PC, Deshpande M, Ranjekar P, Prakash O. Phytochemicals in cancer treatment: From preclinical studies to clinical practice. Vol. 10, Frontiers in Pharmacology. Frontiers Media S.A.; 2020.

24. Pratheeshkumar P, Son YO, Korangath P, Manu KA, Siveen KS. Phytochemicals in cancer prevention and therapy. Vol. 2015, BioMed Research International. Hindawi Publishing Corporation; 2015.

25. Patel MB, Mishra S. Hypoglycemic activity of alkaloidal fraction of Tinospora cordifolia. Phytomedicine. 2011 Sep 15;18(12):1045–52.

26. Stanely Mainzen Prince P, Padmanabhan M, Menon VP. Restoration of antioxidant defence by ethanolic Tinospora cordifolia root extract in alloxan-induced diabetic liver and kidney. Phytotherapy Research. 2004 Sep;18(9):785–7.

27. Hikal WM, Alhawiti LS, St P, Petersburg S, Said-Al Ahl HA, Mahmoud AA, et al. Cissampelos pareira: A potential source of medicine to treat malaria. ~ 37 ~ International Journal of Mosquito Research [Internet]. 2021;8(5):37–43. Available from: http://www.dipterajournal.com

28. Sato M, Maulik G, Bagchi D, Das DK. Myocardial Protection by Protykin, A Novel Extract of trans-Resveratrol and Emodin. Vol. 32, Free Rad. Res.

29. Baba S, Osakabe N, Natsume M, Muto Y, Takizawa T, Terao J. Nutrient Metabolism In Vivo Comparison of the Bioavailability of ()-Catechin, ()-Epicatechin and Their Mixture in Orally Administered Rats [Internet]. 2001. Available from: https://academic.oup.com/jn/article/131/11/2885/4686806

30. —y CM, Morand C, Crespy V, Demigne C, Texier O. Quercetin is recovered in human plasma as conjugated derivatives which retain antioxidant properties.

31. Coughtrie MWH, Sharp S, Maxwell K, Innes NP. Biology and function of the reversible sulfation pathway catalysed by human sulfotransferases and sulfatases. Vol. 109, Chemico-Biological Interactions. 1998.

32. del Rio D, Borges G, Crozier A. Berry flavonoids and phenolics: Bioavailability and evidence of protective effects. Vol. 104, British Journal of Nutrition. 2010.

33. Sharifi-Rad J, Rayess Y el, Rizk AA, Sadaka C, Zgheib R, Zam W, et al. Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications. Vol. 11, Frontiers in Pharmacology. Frontiers Media S.A.; 2020.

34. Sergides C, Chirilă M, Silvestro L, Pitta D, Pittas A. Bioavailability and safety study of resveratrol 500 mg tablets in healthy male and female volunteers. Experimental and Therapeutic Medicine. 2016 Jan 1;11(1):164–70.

35. Hoshino J, Park EJ, Kondratyuk TP, Marler L, Pezzuto JM, van Breemen RB, et al. Selective synthesis and biological evaluation of sulfate-conjugated resveratrol metabolites. Journal of Medicinal Chemistry. 2010 Jul 8;53(13):5033–43.

36. Hoshino J, Park EJ, Kondratyuk TP, Marler L, Pezzuto JM, van Breemen RB, et al. Selective synthesis and biological evaluation of sulfate-conjugated resveratrol metabolites. Journal of Medicinal Chemistry. 2010 Jul 8;53(13):5033–43.

37. Priyadarsini RV, Nagini S. Cancer Chemoprevention by Dietary Phytochemicals: Promises and Pitfalls. Vol. 13, Current Pharmaceutical Biotechnology. 2012.

38. Rizeq B, Gupta I, Ilesanmi J, AlSafran M, Rahman MDM, Ouhtit A. The power of phytochemicals combination in cancer chemoprevention. Vol. 11, Journal of Cancer. Ivyspring International Publisher; 2020. p. 4521–33.

39. Walter H, Consolaro F, Gramatica P, Scholze M, Altenburger R. Mixture Toxicity of Priority Pollutants at No Observed Effect Concentrations (NOECs). Vol. 11, Ecotoxicology. 2002.

40. Zhuang J, Huo Q, Yang F, Xie N. Perspectives on the Role of Histone Modification in Breast Cancer Progression and the Advanced Technological Tools to Study Epigenetic Determinants of Metastasis. Vol. 11, Frontiers in Genetics. Frontiers Media S.A.; 2020.

41. Fofaria NM, Srivastava SK. STAT3 induces anoikis resistance, promotes cell invasion and metastatic potential in pancreatic cancer cells. Carcinogenesis. 2015 Jan 1;36(1):142–50.

42. Das I, Das S, Saha T. Saffron suppresses oxidative stress in DMBA-induced skin carcinoma: A histopathological study. Acta Histochemica. 2010 Jul;112(4):317–27.

43. Lee Y. Cancer chemopreventive potential of procyanidin. Vol. 33, Toxicological Research. Korean Society of Toxicology; 2017. p. 273–82.

44. Naeimi M, Shafiee M, Kermanshahi F, Khorasanchi Z, Khazaei M, Ryzhikov M, et al. Saffron (Crocus sativus) in the treatment of gastrointestinal cancers: Current findings and potential mechanisms of action. Journal of Cellular Biochemistry. 2019 Oct 1;120(10):16330–9.

45. Wang LG, Chiao JW. Prostate cancer chemopreventive activity of phenethyl isothiocyanate through epigenetic regulation (review). Vol. 37, International Journal of Oncology. Spandidos Publications; 2010. p. 533–9.

46. Gupta P, Adkins C, Lockman P, Srivastava SK. Metastasis of Breast Tumor Cells to Brain Is Suppressed by Phenethyl Isothiocyanate in a Novel In Vivo Metastasis Model. PLoS ONE. 2013 Jun 27;8(6).

47. Khor TO, Keum YS, Lin W, Kim JH, Hu R, Shen G, et al. Combined inhibitory effects of curcumin and phenethyl isothiocyanate on the growth of human PC-3 prostate xenografts in immunodeficient mice. Cancer Research. 2006 Jan 15;66(2):613–21.

48. Mukherjee S, Dey S, Bhattacharya RK, Roy M. Isothiocyanates sensitize the effect of chemotherapeutic drugs via modulation of protein kinase C and telomerase in cervical cancer cells. Molecular and Cellular Biochemistry. 2009;330(1–2):9–22.

49. Gupta P, Wright SE, Srivastava SK. PEITC treatment suppresses myeloid derived tumor suppressor cells to inhibit breast tumor growth. OncoImmunology. 2015;4(2):1–8.

50. Dalasanur Nagaprashantha L, Adhikari R, Singhal J, Chikara S, Awasthi S, Horne D, et al. Translational opportunities for broad-spectrum natural phytochemicals and targeted agent combinations in breast cancer. Vol. 142, International Journal of Cancer. Wiley-Liss Inc.; 2018. p. 658–70.