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ROLE OF PLANT-BASED ACTIVE COMPOUNDS IN INFLAMMATORY RESPONSES OF CANCER

Namrata Kahar * and Rohit Seth

Department of Zoology, Guru Ghasidas Vishwavidyalaya, Koni Bilaspur - 495551, Chhattisgarh, India.

Keywords:

Inflammation, Cytokines, Tumour microenvironment, Cancer, Herbal therapy, Inflammatory factor

Correspondence to Author:
Namrata Kahar

Department of Zoology, Guru Ghasidas Vishwavidyalaya, Koni Bilaspur - 495551, Chhattisgarh, India.

E-mail: namratakahar3@gmail.com

ABSTRACT: Cancer is a non-communicable life-threatening disease and a majority of cancers are caused due to inflammatory responses and association with precursor lesions termed as proliferative inflammatory factors. Inflammatory response arises because of dysfunction of anti-oxidative proteins due to DNA damage and may increase oxidative stress. This review mainly focuses on the inflammatory factors which trigger specific pathways inside the cell and create a tumour microenvironment that subsequently leads to cancer induction and progression. We are providing information about the role of various plant derived active compound and their role in treatment of cancer via induction of chronic inflammation and altering the level of reactive oxygen species (ROS). In this review, we will also document currently available treatments and their possible therapeutic implications in ameliorating the ailments that arise due to cancer. In the later section of this review, we have added notes on the challenges that need to be addressed to improve the efficiency of drugs derived from medicinal plants. It appears that herbal therapies are effective for targeting the cellular compartment and effectively correcting the tumour microenvironment and plays a major role inmodulating the inflammatory responses.

INTRODUCTION: Cancer is one of the leading causes of death and poses a threat to mankind [1]. It is the second leading cause of death after cardio-vascular disease [2]. The majority of cancers present some form of inflammation in the beginning that progress and leads to the formation of a tumor. An inflammatory response is the part of the immune system which aids in the survival and proliferation of cancer cells. The cell and inflammatory mediators are the main creators for tumour micro-environment which regulates the pathogenesis of tumour generating cells (tumour growth).

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Researchers have explored the role of inflammation, the immune tumour microenviron-ment and potential immune biomarkers in the progression of cancer where some inflammation is relative to putative cancer precursor lesions, termed as proliferative inflammatory atrophy [3].

It is generated inside the cell because of the dysfunction of anti-oxidative proteins or because of DNA damage that might increase oxidative stress. Together these factors might serve as a drive to carcinogenesis via oxidative stress mechanisms and generation of ROS species induced mutagenesis [4]. This sort of damage in biomacromolecules may form a ferocious cycle of oxidative stress, resulting in cancer development [5]. Where cyclooxygenase has an important role in the induction of inflammation [6-8]. Furthermore, genomic instability, an appropriate phenomenon and alternation in the epigenetic characters such as DNA methylation or

micro RNA dysregulation play a vital role in carcinogenesis, especially in inflammation-related cancer. DNA methylation and his tone post-translation modifications are the most common forms of Epigenetic modifications [9, 10]. Oncogenic changes in cells lead to induction of inflammatory pathways in pre-malignant and malignant cells, which promotes chronic inflammation caused by infections, exposure to irritants, or some other factors, including suffering from autoimmune disease in almost 20% of human cancers [11]. In this review, we will address some of the plant active compounds that can have an effect on inflammation and induce the pathway of the inflammatory response in cancer cells. These inflammatory mediators generated by cancer cell may serve as potential targets for cancer therapy. Furthermore, the mechanism by which inflammation is dysregulated in cancer also provides tumor-promoting signals that may offer new therapeutic opportunities in cancer therapy.

Inflammation and Cancer: Inflammatory responses and cancer generally go hand in hand. Inflammation is a self-activated and controlled mechanism of the immune system to eliminate infections from the body and repairing itself. While dysregulation induces inflammatory disorder it is important to understand inflammation progression from early stage to late stage of cancer.

Here we have elucidated the different inflammation stages in terms of cancer generation. As inflammation progression takes place, and is exemplified by cell injury (bacterial infection, obesity or smoking etc) it induces the activation of tumour micro-environment (TME) which maintain early stage of tumour generation.

Enhanced inflammatory response causes immuno-suppression Certainly the anti-tumour stimulation therapy is beneficial for immunosuppression in an early stage. Several studies have shown that chronic inflammation is observed during the last stage of the excessive proliferation of cancer cells in patients. Different stages of inflammation during the progression of cancer is illustrated in the **Fig. 1**.

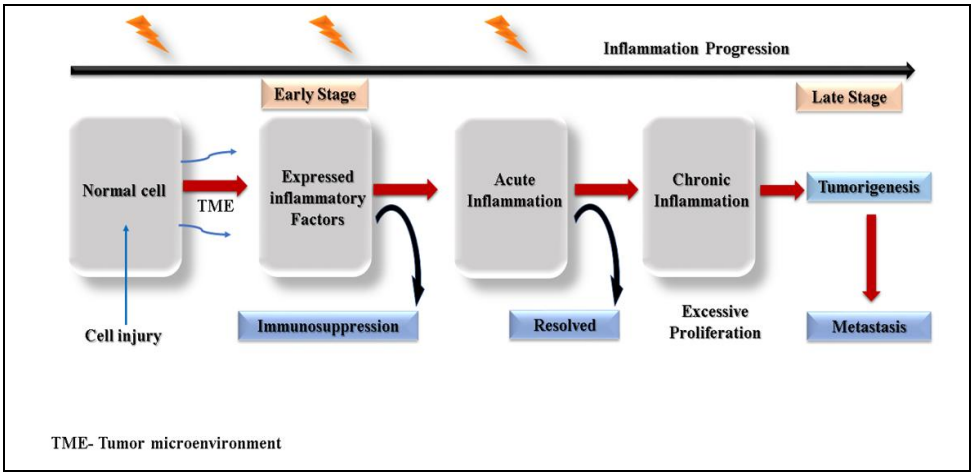

FIG. 1: DIFFERENT STAGES OF THE INFLAMMATION. Any type of injury or cell damage may cause inflammation. These are maintained by the tumour microenvironment, and infiltrative cells play an important role in the early to the late stage of inflammation progression followed by cancer generation. The persistent excessive proliferation causes acute inflammation drives the cell transformation in the late stage if not resolved. At the same time, chronic inflammation accelerates tumorigenesis followed by tumour metastasis. Where chronic inflammation contributes to all forms of human cancer.

Inflammation Inducing Factors:

Do Inflammatory Factors Support or Limit Tumour Growth: As an anti-inflammatory mediator, prostaglandin plays a crucial role in inflammation, whereas cytokines are involved in inflammation. An up-regulated prostaglandin response has been observed in colon carcinoma [12]. Although, there are five primary prostaglandins; prostaglandins D2, prostaglandins E2, prostaglandins F2a, prostaglandins 12, and thromboxane A2. They are biosynthesized by arachidonic acid metabolism [13-18]. After the subsequent conversion of the proteinoids by specific synthases or isomers, it develops the biological activities to regulate immune function like inflammation [19]. Cytokines are important mediators of communication between cells in the inflammatory tumour microenvironment. In the

neoplastic cells generally, over-expression of pro-inflammatory mediators, including proteases, eicosanoids, cytokines, and chemokinesis observed [20].

Several cytokines have been linked with both human and experimental cancer, which can either stimulate or inhibit tumour development such as macrophage migratory inhibitory factor (MIF), Tumor necrosis factor (TNF-α), Interleukins (IL)-6, IL-17, IL-12, IL-23, IL-10 and transforming growth factor (TGF- β). MIF is a major cytokine in many cancers, and there is evidence that this cytokine is produced by both malignant cell and infiltrative leukocytes. Inflammatory processes can promote, or maybe even initiate, or cause malignant disease [21]. While the tumor-suppressor proteins can function as a positive regulator, it stimulates the production of inflammatory mediators. TNF-α signalling can promote cell survival, invasion, and angiogenesis [22].

Its production is associated with increased risk of multiple myeloma, bladder cancer, hepatocellular carcinoma, gastric cancer, and breast cancer, as well as poor prognosis in various hematological malignancies [23]. Tumour-promoting inflammation is considered one of the permissive characteristics of cancer development. Following the initial success of immune therapies that modulate the adaptive immune system, based on preclinical and epidemiological data, it is reported that inflammation and innate immunity are important targets in patients with cancer [24]. Epidemiological studies have suggested some beneficial effects of anti-inflammatory medicines such as aspirin or non-steroidal drugs in protecting against several forms of cancer, especially that of the colon [25]. Aspirin is used as a powerful chemopreventive drug [26-28], as it blocks the prostaglandin production as well as induces the production of endogenous anti-inflammatory mediators [29].

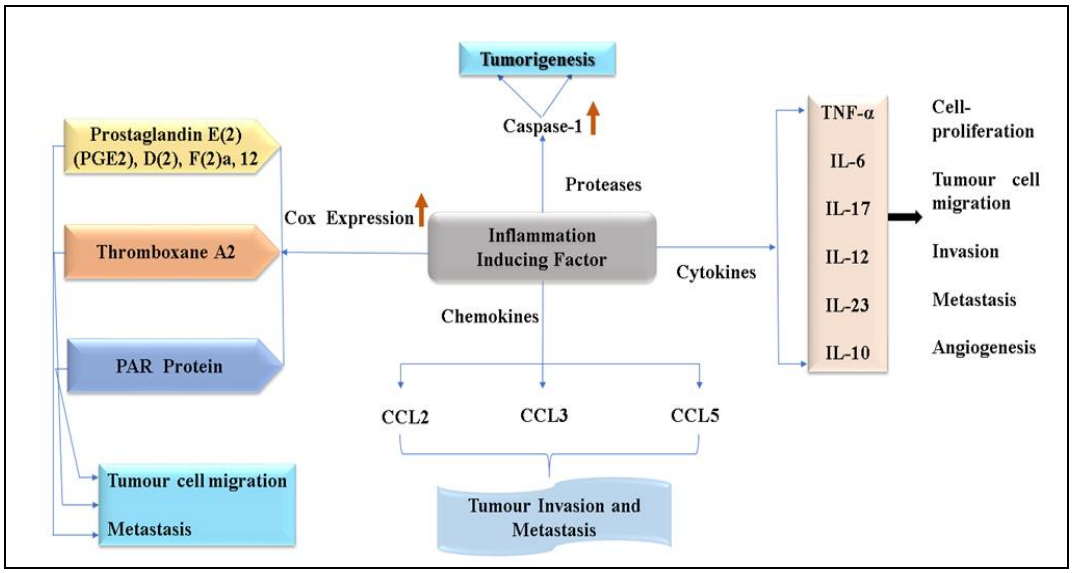

FIG. 2: POTENTIAL INFLAMMATORY FACTORS AND THEIR ROLES IN CANCER GENERATION. Overexpression of different inflammatory factor COX proteins [47, 48, 49], protease, chemokines, and cytokines are responsible for tumour cell progression, tumorigenesis, metastasis and angiogenesis, *etc*. Although these inflammatory factors regulate the immune system. TNF-α 23, IL-6, IL-17, IL-12, IL-23, IL-10 these are cytokines that are responsible for the cancer cell proliferation induces tumour cell invasion, metastasis, and angiogenesis.

In every aspect of carcinogenesis, tumour microenvironment contributes to the most promising target for cancer therapy. Gao F. *et al.* defined tumour microenvironment and also discussed their role in the initiation and progression of cancer [30]. As inflammation is the first line of defense in the immune system thus, not only can inflammation cause cancer, but cancer also leads to inflammation. Inflammatory factors are important for tumour growth **Fig. 2**. Their role depends on the nature of the tumour and inflammatory cell interaction [20], which may produce growth factors for tumour proliferation which in turn creates a tumour microenvironment and provide factors for antitumor immune responses. There are various types of immune cells in filtering cancer and are amajor source of inflammation. This includes natural killer cells, Cytotoxic CD8+ Cells (CTL),

IL-1-producing T helper cells (TH1), TH17, macrophages, monocytes, dendritic cells produce cytokines like IL-1, 6, 17, 23, and TNF. Pro-tumorigenic cytokines include interleukins IL-6, 11, 21, 22 that activates the signal transducer and activator of transcription 3 (STAT3), TNFα, IL-1, 18 that activates Nuclear Factor (NF-κB) and the IL-23 to 17 that activates both STAT3 and NF-κB in tumour cells [31, 32]. NF-κB and STAT3 are essential for inflammation-promoted cancer development [33-36]. Tumour environment is maintained by the infiltrating immune cells and their secreting inflammatory factors. The production of cytokines, chemokines, and extracellular enzymes, infiltrating immune cells may serve as a tumour promoter by supporting the proliferation of tumour cells and inhibiting programmed cell death **Fig. 3**. Tumour infiltrating Macrophages and neutrophils produce IL-6, IL-23, IL-1, and TNFα and activation of Th17 lymphocytes for the production of IL-17, IL-21, IL-22. In contrast, the dendritic cells facilitate T-cell mediated immunity against cancer by IL-12 production and antigen presentation. Th-1 cells further activate the natural killer cell (NK) and cytotoxic T- lymphocytes (CTLs) by secreting IFN-γ. NK cells and CTLs target cancer cells for destruction. Moreover, regulatory T cells (Treg) inhibit pro and anti-cancer immunity by producing IL-10 and TGF-β through the contact depend and independent mechanism [37]. Targeting any of these cellular components of the tumour has emerged as a promising approach and constitutes the basis for anti-angiogenic and anti-inflammatory therapies applied to various types of human cancer [38, 39].

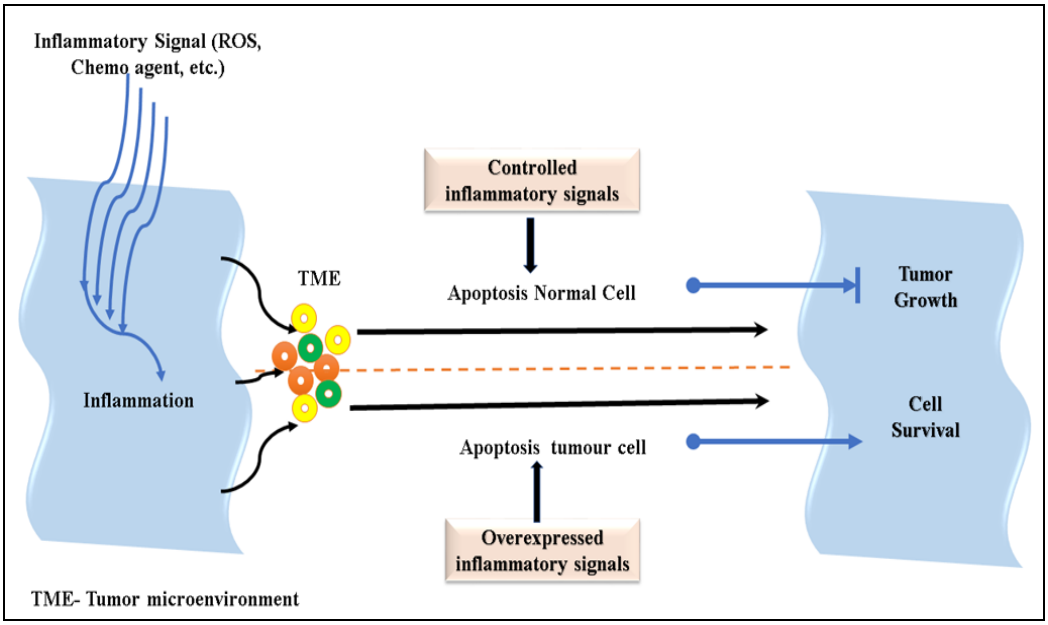

FIG. 3: THE RELATION BETWEEN INFLAMMATION-INDUCED APOPTOSIS AND TUMOUR GROWTH. Reactive oxygen species (ROS) chemotherapeutic agents and other drugs used in cancer therapy can trigger the inflammation signals inside the cell and genesis of tumour microenvironment where the controlled or regulated inflammation induces apoptosis however in the tumour cells apoptosis is inhibited by overexpression of inflammatory signals leading to cell survival.

The Role of Cyclooxygenase In Inflammation: One of the foremost important events of inflammation is the induction of its form (cyclooxygenase, a rate-limiting enzyme), by several stimuli associated with cell activation and inflammation made applicability of finding disease. COX-1 and COX-2 are the two isoforms of cyclooxygenase responsible for the generation of prostaglandins. Although COX-1 is constitutively expressed in all cell types relentlessly, the expression of that protein is substantially higher in tumour than in any of the normal tissues [40-42], and COX-2 has been demonstrated to be active only under the influence of certain stimulating growth factors and cytokines [43- 45]. Immunoblot analysis revealed an extremely high level of COX-2 protein in two tumour samples of colon tumour and breast tumour [46]. Some experiments suggested that the overexpression of COX-2 may not be unique to colon cancer and may be a feature common to other epithelial tumours [46]. For instance, the inducible form of COX-2 is overexpressed in colon tumour

tissues [6-8] and very often overexpressed in early, malignant tissues and several cancer cells including lung, liver, skin, breast, and colon [47-49]. Similarly, prostaglandin is produced more in the human malignant breast cancer tissue than the normal breast tissues [50]. The activity of COX-2-PGE2 signal pathway can suppress Dendritic cells, NKC, T cells, type-1 immunity excluding type-2 immunity which promote tumor immune evasion. Aromatase which is an important enzyme involved in estrogen biosynthesis is another major proliferator of carcinomas in particular the breast cancer.

Reactive Oxygen Species (ROS) and Inflammation: By product of oxygen consumption and cellular metabolism are generally considered as reactive oxygen species (ROS) which are generated by the partial reduction of molecular oxygen [51, 52]. They are continuously generated inside living organisms by different mechanisms [53]. ROS has long been associated with cancer, where different types of tumour cells have shown to produce an elevated level of ROS compared to their normal counterparts. Elevated levels of ROS are thought to be oncogenic, causing damage to DNA, proteins, and lipids, thereby promoting genetic instability and tumorigenesis [54-58]. Oxidative stress caused by chemotherapy is added to the oxidative stress that is inherent in the tumour cell. Tumour cells have an altered redox balance when compared with their normal counterparts [59]. However, investigation and development of novel phototherapeutic agents to detect anti-tumour and free radical scavenging activities become an unmet need. Hence, identifying altered ROS activity as a potential target for cancer therapies [59]. See enclosed **Table 1** for details of plants with their active ingredients and ROS activity.

TABLE 1: DETAILS OF PLANT WITH THEIR ACTIVE PRINCIPLES AND THEIR EFFECTIVE TARGETS

S. no.	Common Name	Botanical Name	Active principles	Effect	ROS Activity	Cancer	Refe
1.	Giant Voodoo Lily	*Sauromatumgigan teum (Engl.) Cusimano & Hett (Typhoniumgigant eum)* (Arecaceae).	Beta-sitosterol, Campesterol, n-hexadecenoic acid, octadecanoic acid	Induces apoptosis	ROS level increased	Gastric carcinoma and liver cancer, hepatocellular carcinoma.	93,94, 95, 96, 105
2.	Giant Voodoo Lily / Typhonium Tuber	*RhizomaTyphonii* (Arecaceae).	Beta-sitosterol, Campesterol, n-hexadecenoic acid, octadecanoic acid	Induces apoptosis	ROS level increased	hepatocellular carcinoma.	96, 105
3.	Garden Stock/ Bromton Stock	*Mathiolaincana* (Bracaecaeae)	Luteolin (LUT)	Induce pro apoptosis Inflammatory markers expression	Antioxidant enzyme activity increases	Renal cell	98, 135
4.	Gukulakanta/ Tamilakanha	*Hygrophila spinosa* (Acanthaceae).	Apigenin and LUT	Induced Cytotoxicity	Antioxidant activity	ovarian and breast cancer cell (MCF-7, MDA MB-231, SKOV-3 cell line)	99
5.	Star anise	*Illicium verum* (Schisandraceae)		Induces apoptosis /Downregulate antiapoptotic genes	_		100
6.	Mulethi (Root)	*Glycyrrhiza glabra* (Fabaceae)		Induces apoptosis/ Downregulate antiapoptotic genes	_		100
7.	Leenseed or Flax	*Linumusita tissimum* (Linaceae)		Induces apoptosis / Downregulate antiapoptotic genes	_		100
8.	Glossy Buckthron	*Rhamnus Frangula* (Ramnaceae)		Downregulate antiapoptotic genes	_		100

9.	Voodoo lily	*Sauromatum venosum* (Araceae)	Lectin	Induces apoptosis	_	Murine cancer cell lines	104
10.	Kariyat, Creat	*Andrographis paniculata* (Acanthaceae)	Andrographolide	Inhibit the proliferation of Tumour cells, enhances TNF- α and induces Apoptosis, increase proliferation of IL-2	_	Colon cancer (HT-29), B16F0 melanoma	106, 107,108
11.	Turmeric	*Curcuma longa* (Zingiberaceae)	Curcumin	Regulates inflammatorycytokines, Induces apoptosis, Inhibits NF- kappa β	Regulates Oxidative stress and activates oxidative enzymes	Carcinoma cancer cell, leukaemia, colon cancer cell	), 136
12.	Kokam	*Garcinia indica* (Guttiferae)	Garcinol, Isgarcinol and Cyanidin-3-glucoside	Induces apoptosis	Inhibit NO radical generation	Human leukaemia (HL-60)	124, 125
13.	Rodent tuber	*Typhoniumflagelliform* (Araceae)	Pheophorbide-a, and methy l-pyropheophor-bide-A	Induces apoptosis, Antiproliferative activity	Antioxidant activity	Lungs cancer (NCI-H23), Breast cancer (HS578T)	126
14	Creeping saxifrage, strawberry saxifrage, creeping rockfoil, mother of thousands, roving sailo	*Saxifragastolonifera* (Saxifragaceae)	Quercetin	Induce apoptosis DNA fragmentation	_	BGC-823 cells.	127
15.	Basil, Sweet basil	*Ocimumbasilicum* (Lamiaceae)	Ursolic acid	Anti-inflammatory, anticancer activity	Antioxidant scavenging activity	Colorectal Adenocarcinoma cells	128, 129
16..	KutkiKardi	*Picrorhizakurroa* (Scrophulariacea)	Apocynin (Iridoid glycoside)	Induces apoptosis, induce cytotoxicity	Inhibit lipid peroxidation , Antioxidant scavenging activity	Human Breast Carcinoma (MDA-MB-435S), Human Hepatocellular Carcinoma (Hep3B), Prostate cancer cell lines (PC-3)	130
17.	Anemone clematis, Indian virgin's bower garol, Geor Bel, Kanguli, Kaunie- Bali	*Clematis montana* (Ranunculaceae)	Lectin	Induces apoptosis	Antioxidant scavenging activity	L929, HeLa, MCF7 and HepG2 cells	131
18.	Ram Tulsi, Wild Basil, African Basil.	*Ocimumviride* (Lamiaceae)	Thymol, Ursolic acid	Induces apoptosis	Antioxidant scavenging activity	Human colorectal adenocarcinoma cells COLO 205 cells	128, 129
19.	Velame' and Velamebranco	Macrosiphonialongiflora (Des) (Apocynaceae)	Ellagic acid	Anti-inflammatory inhibition of IL-1β, IL-10	Nitric oxide releases	RAW 264.7 cells	132
20.	Red oil palm	*Elaeisguineensis* (Arecaceae).	Tocopherols, tocotrienols, their isomers and carotenoids	Inhibitory action	Scavenging free radicals or ROS, effect on lipid peroxidation	Human breast cancer cells	133
21.	Black Seed	*Nigella sativa*	Melanin	Inhibits MAPK pathway through TLR4	Increased ROS and decreased and Glutathione levels	Colorectal, Adenocarcinoma HT 29 and mCRC SW620 cell lines	134

Cancer and Inflammatory Pathways: Several signalling pathways are involved in the regulation of inflammatory actions during cancer. One such pathway is the TGF-β pathway, TGF-β is very efficient in regulating fundamental cellular processes such as growth, differentiation, or apoptosis. Although sporadic mutations in TGF-β and its pathway are not very common in colorectal cancer, pancreatic cancer, and their degree is different in other types of cancers [60]. Hence, it is not suggested as a significant prognostic marker [61]. The transcription factor, NF-κB, has a role in proliferation, cell survival, and regulation of the cell cycle and in the development of resistance to drug therapies [62-64]. Researchers have indicated that the microenvironment of the tumour, especially fibroblasts, secretes a Want family member Wnt-16B through the NF-κB-dependent pathway, thereby mediating the reduction of chemotherapy-induced programmed cell death in the prostate cancer [65] cell and is also associated with pancreatic cancer [66-68] and up-regulated in lung [69]. Recently, a form of programmed necrosis has also been identified [70]. Activation of the death receptor can lead to caspases- independent cell death termed necroptosis. While the necroptosis is induced by the TNF-family of cytokines and mediated by the kinases RIP1 and RIP3 in the absence of the caspases-8 activation, RIP1 forms a complex with the key regulator of necroptosis, RIP3, and its downstream substrate, MLKL [71]. TNFα was frequently detected in human cancer (produced either by epithelial tumour cells, as in, for instance, ovarian and renal cancer) or the stromal cell (as in Breast cancer) [72]. Not only the intracellular or extracellular protein elevates the inflammatory response, but intracellular ions also contribute. It is also reported that inflammatory responses are inhibited by magnesium through downregulation of TLR4/NF-kB, activation of phosphoinositide 3-kinase (PI3K)/Akt pathway or the inhibition of HMGB1 secretion [73-75]. These key molecules may serve as potential markers for prognosis of various cancers.

Currently Available Treatments: Despite the intense investigation /trial of the potential anti-cancer drugs, current therapies are not effective in treating most forms of cancer. The major reason for this potential failure is the occurrence of drug resistance. Increasing evidence suggests that the tumour microenvironment plays a critical role in the resistance of tumour cells to both targeted therapy and DNA damaging chemotherapy [76]. At present, several treatment options are available depending on the cancer stages, such as targeted therapies, immune therapies, cancer vaccines, chemotherapy, radiation therapy, and surgery. If we focus just on chemotherapy, this is the process through which synthetic drugs used for curing cancer are introduced into the patient, and it is a very painful procedure. Recently, WHO studies reported that about 55% of patients suffer pain, and this experience is very unpleasant and also affects emotional health during, before, and after treatment. A lot of cancer victims would preferably use other treatment methods that are less painful but are as effective. The cost of treating cancer in most of hospitals is discouraging to patients and making cancer victims more traumatized. Modern technology for cancer detection is more efficient and precise than the past methods used, which are time-consuming and too general. Majority of cancer patients still rely on the use of chemotherapeutics.

Chemotherapy drugs like Gemcitabine and Folfirinox (oxaliplatin, irinotecan, fluorouracil, and leucovorin) are widely used for the treatment of metastatic pancreatic cancer (MPC). It has been recently studied that nab-paclitaxel plus gemcitabine (nab-p/gem) significantly improved overall survival, progression-free survival, and response rate in patients with metastatic pancreatic adenocarcinoma, and as compared with that, FOLFIRINOX WITH NAB-P/GEM treatment has been observed with an increased survival advantage and toxicity [77]. In contrast, Ruxolitinib is also a potent JAK1/JAK2 inhibitor that has shown clinical benefit in patients with myelofibrosis, a myeloproliferative neoplasm characterized by cachexia, weight loss, elevated pro-inflammatory cytokines, and dysregulated JAK/STAT signaling [78-80].

Among them, cisplatin is also a potent chemotherapeutic drug which has been used over the last 25 year. However, it causes nephrotoxicity in many ways [81]. Acute kidney injury (AKI) is one of the most serious and more common complications **Fig. 4**. Which occurs in 20-30% of patients. It has been studied that cisplatin induces

increased expression of several chemokines and cytokines responsible for the inflammation. For example, the expression of IL-1β, IL-18, CX3CL1, and IL-6 are increased as a result of cisplatin nephrotoxicity [82, 83]. While *in-vivo* deletion of caspase 1 is responsible for the formation of active IL-1β, IL-18 reduces cisplatin kidney injury and neutrophil infiltration [84-86]. Cisplatin nephrotoxicity also contributes to significant upregulation of IFN-γ expression, but neutralizing antibodies to IFN-γ provided no protection against renal injury [87, 88]. Doxorubicin is another potent drug that is used to treat many cancers but patient receiving this drug are reported to develop heart attack [89-91].

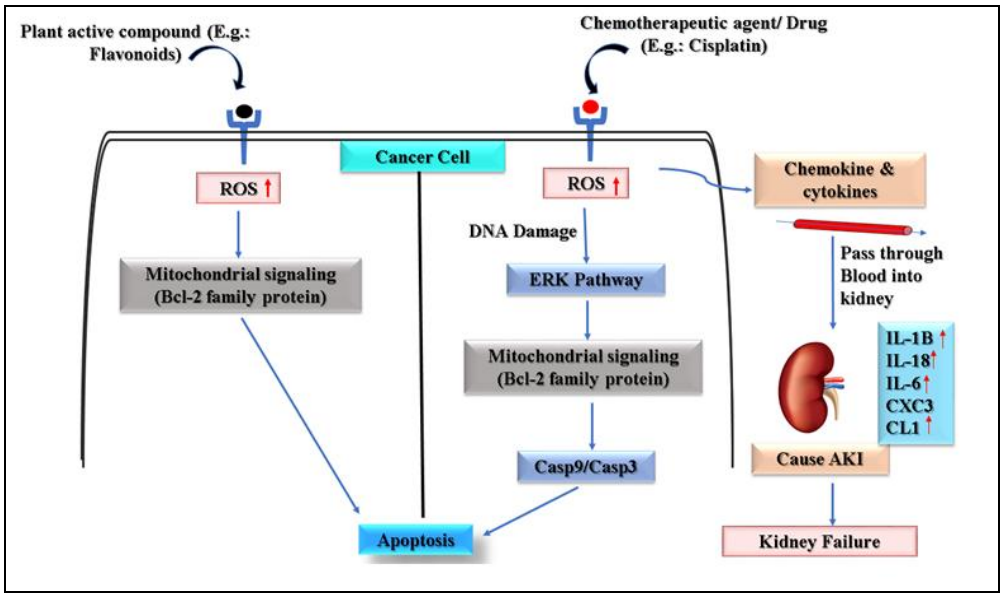

FIG. 4: UNDERLYING MECHANISMS OF DIFFERENT PATHWAY SUTLILIZED BY CHEMOTHERAPEUTIC DRUGS AND NATURAL PLANT DERIVED COMPOUNDS. Both chemotherapeutic drugs and plant derived compounds trigger subsequent cytoplasmic signals leading to induction of apoptosis in the cancer cell. Chemotherapeutic agents or drugs (e.g. cisplatin) inhibits proliferation of cancer as well as normal cell whereas the plant active compound inhibits cancer proliferation. Comparison of plant based compounds and chemotherapeutic drugs suggest multiple side effects of the chemotherapeutic drugs (for example Cisplatin) like AKI Acute kidney injuryand increased expression of some specific inflammatory marker (INF, IL- 18. IL-6 *etc*.) even in normal cells apart from cancer cells.There are also chances of other harmful effects of these treatments *viz.* second cancers after chemotherapy [92]

Active Herbal Compounds Mediating Inflammatory Responses: We are currently in that era where chemotherapeutic drugs are used for the treatment of cancer and despite several contraindications, most of the patients largely rely on chemotherapy. Active herbal compounds hold promise for the treatment of malignancies, although the plant constituents have become a promising source of active natural products which differ widely in terms of their biological and structural properties. These compounds are less exploited in terms of treatment for various types of cancers. Herbal drugs are also known to have good immune-modulatory properties which act by stimulating both non-specific and specific immunity [93].

In recent years, the prevention of non-communicable diseases such as cancer and many disorders is found to be associated with the ingestion of fresh fruits, vegetables, tea, or plant beverages that are rich in natural antioxidants [94, 95]. The therapeutic potential of plant products is due to the presence of several compounds having distinct mechanisms of action; some of them are enzymes and proteins while others are low molecular weight compounds such as vitamins, anthocyanins, carotenoids, flavonoids and other phenolic compounds. The reason for investigations on the medicinal plant is the ethnobotanical knowledge which still exists in remote parts of the world [96] and these plants are used by regional healers for ameliorating the ailments.

Several plant active compounds have shown immunomodulatory activity through their interaction with specific surface receptors and show specific mechanism of action. These potential mechanisms trigger the secretion of inflammatory factors causing the death of cancer cell by a mechanism called apoptosis.

Therapeutic Implications of Plant-Derived Active Compounds in Cancer: Once a better insight about the action of the plant products is achieved at the cellular and biochemical level, it could be possible to make a better assessment of what other agents (*e.g.,* synthetic compounds) may interact with plant active compounds in a synergistic and antagonistic manner. This provides a better understanding and a good prediction as to which combination would be successful. For appropriate understanding, both cell lines and animal models should be employed. Several natural products are effective in accelerating wound healing by stimulating the different growth factors and cytokines. They may have fewer side effects and represent a cost-effective substitute [97, 98] to synthetic drugs. *Sauromatum giganteum* (Engl.) Cusimano and Hetttuber have been used to treat many kinds of cancer, such as gastric carcinoma and liver cancer. Experimental studies suggest that SFE-CO_2 extract from *Sauromatum giganteum* (Engl.) Cusimano and Hetttuber could induce apoptosis in tumour cells [99].

The extract showed significant increases in reactive oxygen species on SMMC-7721 cell lines, where the caspases-3 & caspases -9 have risen in Western Blotting analysis. Ultimately the SFE-Co2 extract from *Sauromatum giganteum* or *Typhonium giganteum* induced the apoptosis [99]. The up-regulation of TRAIL/ TRAIL-R1 and TRAIL-R2 by lignans of Rhizoma Typhonii could be involved in the induction of apoptosis [100]. But it is unclear whether decoction or Vinum had a better curative effect [101]. Recently, Albarakatim *et al.* (2020) reported that luteolin (LUT), a plant-derived compound, provide significant protection against lead acetate (PbAc)-induced renal injury in rats. PbAc significantly lowers the level of antioxidant enzyme activity and expression (SOD, CAT, GPx, GR, and MDA). PbAc exposure down-regulated Nfe 212 and Homx1 mRNA expression and significantly increased inflammatory marker (TNF-α, IL-1β, and NO) levels in renal tissue. It is also reported that down-regulated Nfe212 and Homx1 mRNA expression significantly increase levels of inflammatory markers (TNF-α, IL-1β, and NO) in the renal tissue. All these factors together up-regulated the synthesis of pro-apoptotic proteins and down-regulated anti-apoptotic protein expression. Notably, LUT pre-treatment of PbAc -treated rats provides significant protection against PbAc intoxication *via* anti-inflammatory, anti-oxidant, and anti-apoptotic activities by triggering the activities of the Nrf2/ARE signalling pathway [102]. It is also reported that antioxidant-enriched fraction (AEF) of *H. spinosa* from the whole plant is rich in the presence of apigenin and LUT, which exerted dose-dependent anticancer potential against both ovarian and breast cancer cell lines with a low level of IC_{50} (43 μg/ml) in SKOV-3 cell line [103]. *Illicium verum, Glycyrrhiza glabra, Rhamnus Frangula,* and *Linum usitatissimum* extracts have shown reduced *in-vitro* tumour cell proliferation significantly and using MTT assay and RT-PCR analysis suggested that these extracts could be employed as chemotherapeutical adjuvants for different cancer treatments [104].

Hence, it is very important to identify the component of plant extract causing cell cytotoxicity and inhibiting the cell viability leading to apoptosis. So, it is very clear that we need to take one more step out of this current treatment scenario and investigate new diagnostic, therapeutic improvement, thereby subsiding the side effects of chemotherapy that are often difficult to ameliorate and can significantly impair a cancer patient's quality of life, in both early-stage and late stage of cancer.

Several studies described here and elsewhere provide convincing evidence regarding the antitumor and anticancer activities of plant products like lectins. These scientific findings, together with evidence for their therapeutic activity against cancer [105, 106]. Singh Bain and colleges have been reported that SVL (*Sauromatum venosum lectin*) showed significant inhibition toward the various cancer cell lines [107]. Based on the results they suggested that this plant lectin has antiproliferative response-ability which may help in the identification of new lectin probe for detection and study of certain types of cancer. The effect of aqueous extract of *Typhonium giganteum* in hepatocellular carcinoma SMMC-7721 cells gene expression is reported by Wang SQ [108]. The Elevated level of IL-2 estimated using DUOSET-ELISA kit has shown in cancer cell line from dichromethen fraction of *Adrographispaniculata* extract [109–111]. In general medical practice, phytopharmaceuticals play an important role for the

treatment of diseases of the cardiac and vascular system [112], nervous system [113], and immune system [114] and a huge number of herbal drugs have suggested prophylactic effect besides their therapeutic use for disease [115, 116]. Although, the annual report of CDC, NCI stated that overall cancer death rates declined for women, men, children and young one and researchers look forward to treat common cancers of lung, prostate, breast and colorectal cancer. List of some important plant-derived materials used for treatment of different cancers are mentioned in **Table 1**.

Major Challenges to Improve the Anticancer Properties of Plant Active Candidates: Several studies have reported that anticancer drugs act through the introduction of apoptosis and induce inflammation in human cancer in vitro; not only they exhibit the cancer cell death; they exhibit the anti-angiogenesis [117, 118], anti-metastasis [119, 120] and differentiation [117, 121, 122]. Plant lectins have been extensively utilized for the specific targeting of immunotoxins [123]. The environment factors (temperature, humidity), harvest and postharvest procedure also impact on the quality of plant extracted compound employing various extraction methods (using different extraction solvents, their concentration and ratio) [124]. This is a very essential process in establishing the quality of drug obtained from the plant extract. Moreover, one must bear in mind that not only experiments evaluating the toxicity levels but also most regulatory parameters should be considered before establishing the new idea of the therapeutic process. Any other type of toxic effect, that might result from interactions of various compounds in the plant extract and their effects on different types of cells and tissues should also be examined. Appropriate control groups should be incorporated in most of the toxicity testing studies. Another major challenge that one may encounter is due to the short half-life of many herbal compounds of therapeutic importance. One may enhance the potential of plant extracts by identifying the active compounds and creating a nanoparticle to increase specificity and sensitivity of the compound.

CONCLUSION AND FUTURE PERSPECTIVE: The herbal medicine is a rational medicine among them some of the herbal medicines are in the clinical trials and have shown very good efficacy. Investigating the mechanism of action of herbal medicine in killing the cancer cell without compromising the normal cells is of interest to most of the researchers working in this area. Several studies provide convincing evidence regarding the antitumor and anticancer activities of different plant products. Most of the modern therapies including immunotherapy, radiation therapy, CART cells and combination therapy are widely practised and represent one thing in common that is “inflammatory responses”. As we understand how the inflammation and cancer go hand in hand there is the vast role of TME (tumour microenvironment) to create a strong correlation between inflammation and cancer generation. Tumour environment is maintained by the infiltrating immune cells and their secreting inflammatory factors. Which activates different essential signal transducers and transcriptional factors to generate inflammation promoted cancer.

To promote the use of herbal plant medicine, multicentric large scale clinical trials should be promoted **Fig. 5**. It is essential to identify the right stage of cancer and treatment should be designed accordingly. If clinicians can provide herbal treatment /supplement at an early stage of cancer, treatment will be more efficacious when compared with the late stage of cancer. There are several instances of cancer reoccurrence even after using a chemotherapeutic drug hence herbal supplements may be provided to the patients. Providing herbal medicines may improve the quality as well as the life span of patients. It is essential to dig deep into the ancients wisdom that is available in the literature and also contact regional healers that are located in different parts of the country to learn the use of herbal medicines. Newer researches should focus on increasing the life span and quality of life of patients suffering from cancer. Use of active biomolecules such as nanoparticle may revolutionize the use of herbal medicines. It is evidenced by the published work that such nanoparticles may improve the efficacy of the drug and also subside complications like nephrotoxicity [102, 125, 126]. It is a high time to develop methods and technology to improve the use of plant active compounds in the treatment as well as improving the quality of life of patients suffering from cancer. In this review, we have tried to understand the use of plant-derived active compounds and their effect

on cancer and inflammation. We need to employ multicentric clinical trials for plant medicines to achieve this aim. More researches should be done and funding from governmental and non-governmental agencies should pour in to support the cause.

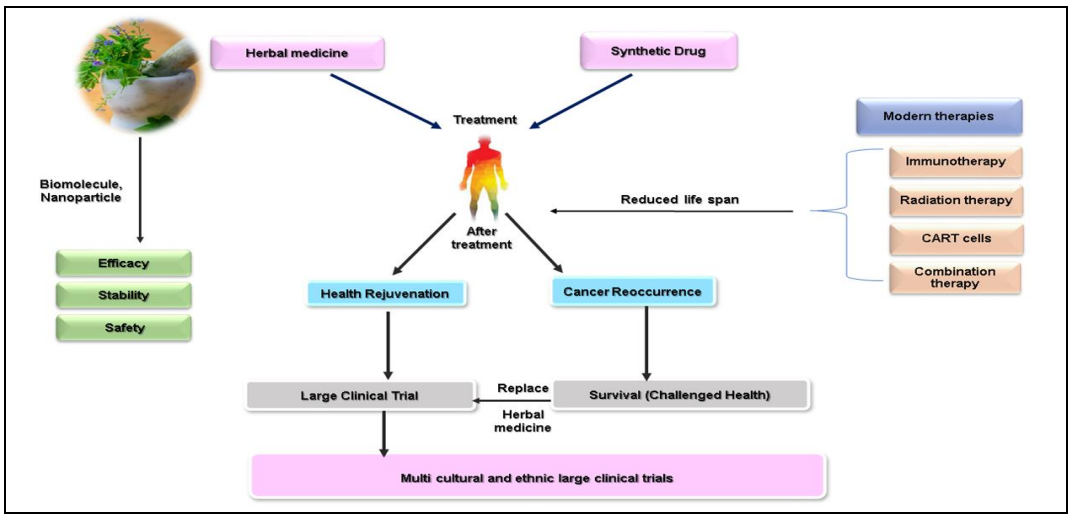

FIG. 5: FUTURE PROSPECTS OF HERBAL MEDICINE IN THE TREATMENT OF CANCER. Using herbal medicine as a treatment option can be considered farely safe in comparison to conventional synthetic drug treatments. Nowadays, several techniques are available to improve the half life of herbal medicines and increasing the shelf life. The improvement of method of analysis and quality control of herbal drugs and medicine along with advancement in clinical trials will certainly increase their efficacy and safety bringing the value of life and health rejuvenation of cancer patients.

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Author's Contribution:

Namrata Kahar: Literature review, manuscript drafting, preparation of figure, concept and design the study.

Rohit Seth: Literature review, manuscript editing and approval of the final version of the manuscript.

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