Evaluation of Toxicity in the Combined Anticancer Potential of Pomegranate and Turmeric: A Comprehensive Study

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KEYWORDS
Pomegranate (Punica granatum), Turmeric (Curcuma longa), Anticancer properties, Phytochemicals, Drug interactions

ABSTRACT:

Aim:
The aim of this review is to investigate the potential of two natural substances, pomegranate (Punica granatum) and turmeric (Curcuma longa), in cancer therapy by evaluating their phytochemical composition, mechanisms of action, and safety profiles.

Objective:
The objective is to highlight the therapeutic properties of pomegranate and turmeric, specifically focusing on their ability to induce apoptosis, reduce cell proliferation, suppress angiogenesis and metastasis, and their anti-inflammatory, antioxidant, and anti-proliferative effects. Additionally, the review aims to assess their therapeutic synergy in preclinical studies and identify possible safety concerns, especially regarding drug interactions.

Purpose:
The purpose of this review is to provide a comprehensive understanding of the anticancer potential of pomegranate and turmeric and to explore their role in enhancing cancer treatment while minimizing toxicity. The review also aims to emphasize the need for further clinical studies to validate their efficacy and safety in diverse patient populations.

Conclusion:
The review concludes that pomegranate and turmeric show promising therapeutic efficacy in cancer treatment due to their bioactive compounds with antioxidant and anticancer properties. Their combined use may enhance therapeutic outcomes, but further clinical research is necessary to confirm their safety and efficacy in clinical settings. Caution is advised regarding potential drug interactions, particularly with cytochrome P450-dependent medications.

Introduction:

Millions of people die from cancer each year, making it a major global health concern. Traditional treatments, such as chemotherapy and radiation, are frequently linked to serious side effects and limited effectiveness in certain cancers, underscoring the need for new, safer therapeutic approaches. Natural compounds derived from plants have drawn attention because of their potential for treatment and comparatively lower toxicity profiles; of these, turmeric (Curcuma longa) and pomegranate (Punica granatum) have been thoroughly researched for their anticancer properties. This review will examine their combined effects, underlying mechanisms of action, and safety profiles.

Phytochemical Composition and Anticancer Properties:

Pomegranate extract has been shown to induce apoptosis, arrest the cell cycle, and inhibit tumor growth in a variety of cancer models, including aprostate and breast cancers. Pomegranate contains polyphenols, flavonoids, and tannins, which contribute to its antioxidant and anticancer effects. The main bioactive compounds, such as ellagic acid, ellagitannins, and anthocyanins, have the ability to modulate key cellular pathways involved in cancer progression.[1] Because of its anti-inflammatory, antioxidant, and anti-proliferative qualities, curcumin—the primary active component of turmeric—has been demonstrated to have anticancer benefits. By altering multiple signaling pathways, including nuclear factor-kappa B (NF-κB),

mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase/Akt (PI3K/Akt), curcumin prevents the growth and spread of cancer cells.[2]

Mechanisms of Action:

1. Induction of Apoptosis:

It is well known that turmeric and pomegranates encourage cancer cells to undergo apoptosis. It has been demonstrated that polyphenols produced from pomegranates activate caspase-mediated cell death by upregulating pro-apoptotic proteins (Bax) and downregulating anti-apoptotic proteins (Bcl-2).[3] By blocking NF-κB and triggering p53, a tumor suppressor protein involved in cell cycle regulation, curcumin causes apoptosis.[4]

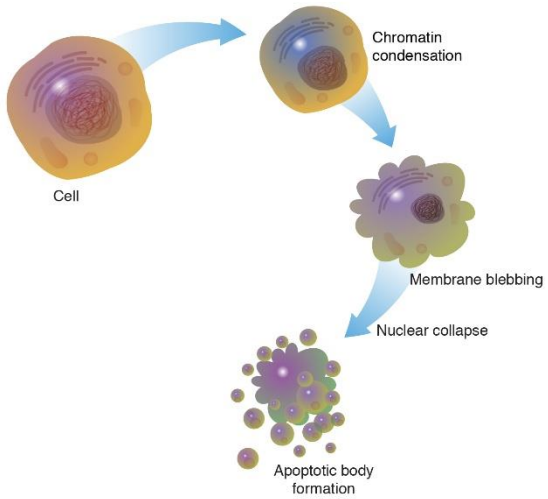

Figure. 1: Cell Apoptasis

2. Cell Cycle Arrest:

At distinct stages, these natural substances cause cell cycle arrest. By modifying the amounts of cyclin and cyclin-dependent kinase, pomegranate extract has been shown to stop the G2/M phase in prostate cancer cells.[5] By downregulating the production of cyclin D1 and cyclin E, two essential regulators of cell cycle progression, curcumin suppresses the cell cycle at the G0/G1 phase.[6]

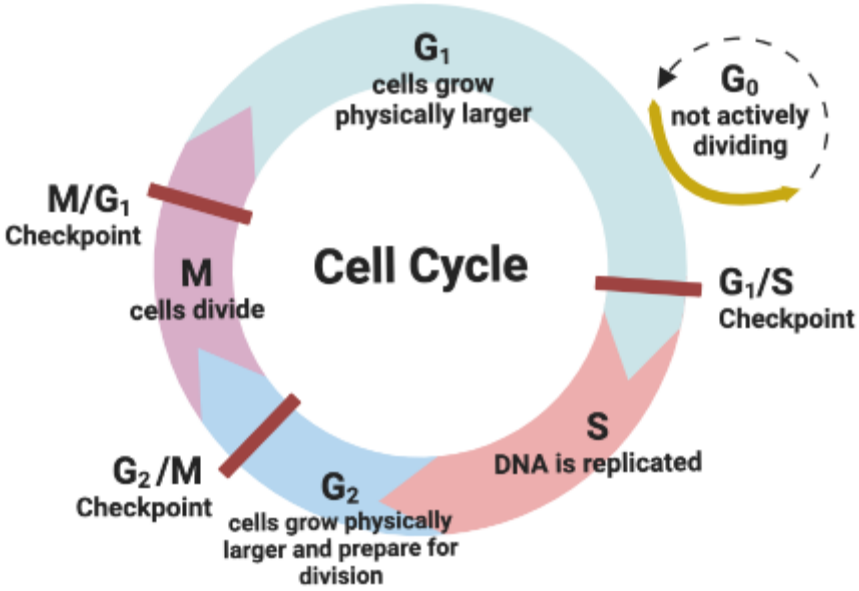

Figure. 2: Activities of Cell Phases

3. Inhibition of Angiogenesis and Metastasis:
By downregulating matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF), respectively, pomegranate and curcumin inhibit angiogenesis and metastasis.[7] Curcumin inhibits the epithelial-to-mesenchymal transition (EMT), a step essential for metastasis, while pomegranate extract, in particular, has demonstrated the capacity to lessen the invasive potential of cancer cells.[8]

4. Modulation of Inflammatory Pathways
The development of cancer is significantly influenced by chronic inflammation. Through their inhibition of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-6, IL-8), pomegranate and turmeric both have anti-inflammatory properties. Curcumin's function in lowering inflammation-driven carcinogenesis is further supported by its capacity to inhibit cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS).[9]

Combined Effects of Pomegranate and Turmeric
Pomegranate and turmeric together have the ability to work in concert. Because of their complimentary methods of action, studies have shown that using both together increases anticancer efficacy. Curcumin and pomegranate polyphenols, for example, were shown to boost the inhibition of prostate-specific antigen (PSA) levels in individuals with prostate cancer, indicating a more substantial reduction in tumor progression.[10]

Safety Profiles
It is generally accepted that taking pomegranate and turmeric as dietary supplements is safe.

- **Pomegranate**: Despite being generally tolerated, it may interact with drugs like statins and anticoagulants that are broken down by cytochrome P450 enzymes.[11]
- **Turmeric**: With few minor adverse effects, such as gastrointestinal distress at large dosages, curcumin is regarded as safe. However, there have been worries about lead contamination in some turmeric products, which makes using high-quality sources necessary.[12]

1. Phytochemical Composition

1.1 Pomegranate:

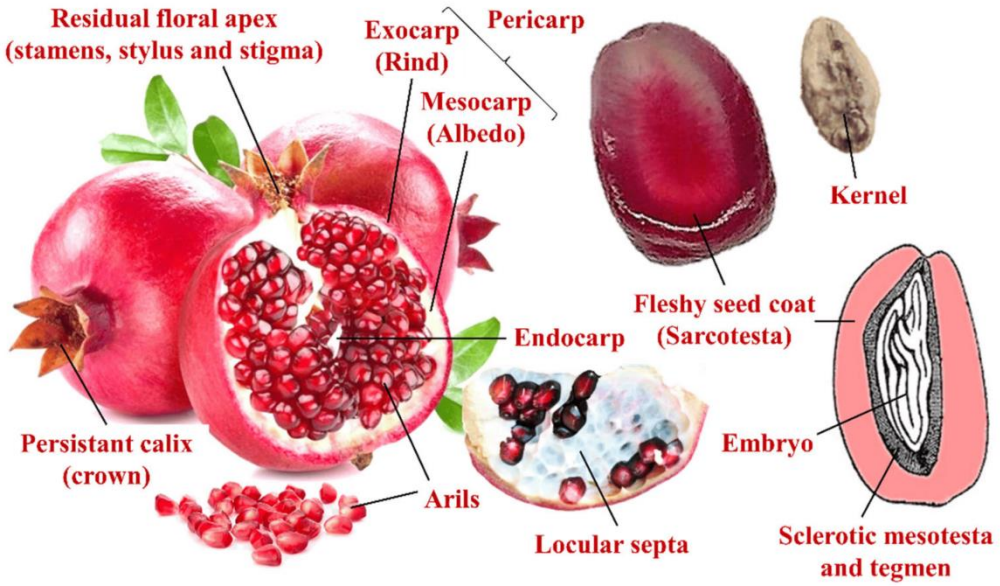

Figure. 3: Pomegranate Anatomy

A potent source of bioactive substances, pomegranates (Punica granatum) are mainly high in polyphenols, which include flavonoids, ellagic acid, anthocyanins, and punicalagins. The most prevalent ellagitannin, punicalagins, are well-known for having an exceptional antioxidant potential that far beyond that of many other dietary sources. These substances are essential in mediating the health advantages of pomegranate consumption, especially in the prevention and treatment of cancer.[13]

Antioxidant Properties:
Strong free radical scavengers, punicalagins and anthocyanins lessen oxidative stress, a major contributor to the development of cancer. Oxidative stress causes protein modification, lipid peroxidation, and DNA damage, all of which aid in the development of tumors. Pomegranate extracts have been demonstrated in studies to dramatically lower reactive oxygen species (ROS) levels in cancer cells, which in turn prevents the cells from proliferating.[14]

Anti-inflammatory Effects:
One of the main indicators of the onset and spread of cancer is persistent inflammation. Pro-inflammatory cytokines such cyclooxygenase-2 (COX-2), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are suppressed by pomegranate polyphenols. Punicalagins decrease the tumor microenvironment's support for cancer cell survival and metastasis via modifying inflammatory pathways.[15]

Anticancer Mechanisms:
Punicalagins and anthocyanins have demonstrated several mechanisms of anticancer action:

1. **Induction of Apoptosis**: By boosting the Bax/Bcl-2 ratio and activating caspase-dependent pathways, which are important apoptosis regulators, these substances encourage cancer cells to undergo programmed cell death.[16]
2. **Inhibition of Cell Proliferation**: Pomegranate extracts inhibit the development of cancer cells by causing cell cycle arrest, especially during the G2/M phase. Cyclins and cyclin-dependent kinases are downregulated in order to accomplish this.[17]
3. **Angiogenesis Inhibition**: By suppressing the expression of vascular endothelial growth factor (VEGF), polyphenols lessen the development of new blood vessels that provide tumors with nourishment.[18]
4. **Anti-metastatic Activity**: By altering matrix metalloproteinases (MMP2 and MMP9) and strengthening tissue inhibitors of metalloproteinases (TIMP), pomegranate chemicals prevent the migration and invasion of cancer cells.[19]

Synergistic Effects with Other Natural Compounds:
Pomegranate and other bioactive substances, like turmeric's curcumin, have been demonstrated to work in concert. For example, research using pomegranate polyphenols in conjunction with curcumin has shown improved suppression of prostate-specific antigen (PSA) levels and tumor growth in prostate cancer models.[20]

Safety and Bioavailability:
Because punicalagins are poorly absorbed in the gastrointestinal tract, their bioavailability is still a problem despite their many advantages. Urolithins, on the other hand, are produced by their metabolism in the gut and are easily absorbed while maintaining their bioactive qualities. Although pomegranate extracts are generally safe, it is important to take into account potential interactions with drugs that are processed by cytochrome P450 enzymes.[21]

1.2 Turmeric:

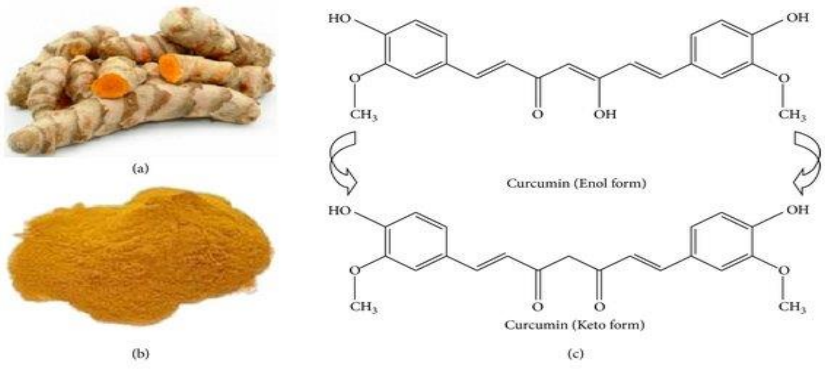

Figure. 4: Turmeric, Curcumin and its chemical structure

The polyphenolic component curcumin is the main source of the medicinal benefits of turmeric (Curcuma longa), a mainstay of traditional medicine. The pharmacological characteristics of curcumin, which makes up 2–8% of turmeric rhizomes, have been well investigated. Because of its distinct chemical structure, curcumin has the ability to interact with a variety of molecular targets within cancer cells, resulting in its bioactivity.[22]

Antioxidant Properties:

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) can be neutralized by curcumin, a strong antioxidant. Curcumin shields proteins, lipids, and DNA from harm by lowering oxidative stress, which stops mutations that might cause cancer. Curcumin's antioxidant properties are further enhanced by studies showing that it increases the activity of natural antioxidant enzymes such glutathione peroxidase, catalase, and superoxide dismutase (SOD).[23]

Anti-inflammatory Effects:

One of the most important factors in the development and spread of cancer is inflammation. By blocking important inflammatory mediators such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and nuclear factor-kappa B (NF-κB), curcumin demonstrates potent anti-inflammatory effect. Curcumin inhibits the inflammatory milieu that promotes tumor development and metastasis via altering several mechanisms.[24]

Anticancer Mechanisms

Curcumin has shown diverse anticancer effects via a number of mechanisms:

1. **Induction of Apoptosis**: Curcumin alters both internal and extrinsic apoptotic pathways, which results in programmed cell death. It suppresses anti-apoptotic proteins like Bcl-2 and Bcl-xL while increasing the production of pro-apoptotic proteins like Bak and Bax.
2. **Cell Cycle Arrest**: Through the downregulation of cyclins and cyclin-dependent kinases (CDKs), curcumin causes cell cycle arrest at the G1/S and G2/M phases. This inhibitor stops malignancies including lung, breast, and colon from proliferating unchecked.[26]
3. **Inhibition of Angiogenesis**: Curcumin reduces tumor angiogenesis by downregulating vascular endothelial growth factor (VEGF) and other pro-angiogenic factors, cutting off the blood supply necessary for tumor growth.[27]
4. **Suppression of Metastasis**: By inhibiting matrix metalloproteinases (MMPs), curcumin reduces the invasive capabilities of cancer cells. It also blocks epithelial-to-mesenchymal transition (EMT), a key process in metastasis.[28]

Synergistic Potential with Other Agents

Curcumin’s ability to enhance the efficacy of conventional cancer therapies, such as chemotherapy and radiotherapy, has been well-documented. For example, it sensitizes cancer cells to paclitaxel and cisplatin, improving their therapeutic outcomes. Additionally, curcumin has demonstrated synergistic effects when combined with natural compounds like pomegranate polyphenols, further enhancing its anticancer potential.[29]

Challenges and Solutions

The limited bioavailability of curcumin, which is caused by poor absorption, fast metabolism, and systemic elimination, presents difficulties for its clinical use. To get around these restrictions, innovative delivery methods such liposomes, nanoparticles, and curcumin conjugates have been created. Curcumin's stability and bioavailability are greatly increased by these preparations, increasing its potential as a medicinal agent.[30]

Safety Profile

At high dosages, some adverse effects like gastrointestinal distress have been documented, although curcumin is generally thought to be safe. Even at dosages as high as 12 grams daily, preclinical and clinical research have confirmed its safety profile. However, in therapeutic circumstances, its interactions with medications like anticoagulants should be closely watched.[31]

2. Mechanisms of Anticancer Action:

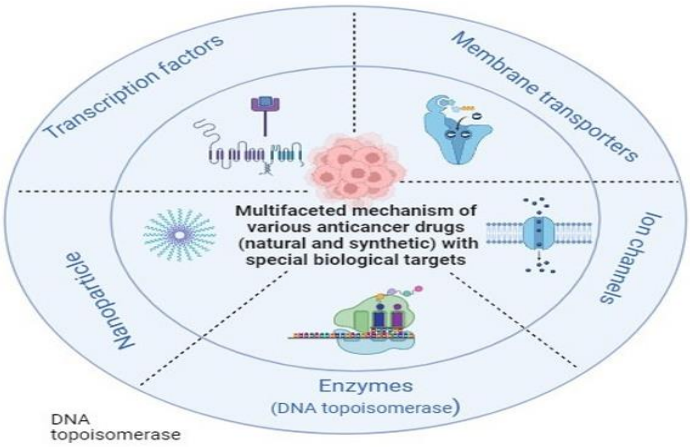

Figure. 5: Understanding the mechanisms underlying anticancer medications that target particular biological targets and signaling pathways

2.1 Pomegranate:

Induction of Apoptosis:

Pomegranate extracts have a strong ability to trigger apoptosis, which is essential for killing cancer cells. Both intrinsic and extrinsic apoptotic mechanisms are activated to accomplish this. Pomegranate polyphenols alter the expression of Bcl-2 family proteins in the intrinsic pathway by downregulating anti-apoptotic proteins like Bcl-2 and upregulating pro-apoptotic members like Bak and Bax. They simultaneously activate two crucial mediators of apoptotic cell death, caspase-9 and caspase-3. The efficient removal of cancer cells is ensured by this dual regulation. Pomegranate-derived chemicals have been shown to significantly induce apoptosis in studies using models of breast and prostate cancer.[32] Pomegranate polyphenols increase the activity of death receptors like Fas in the extrinsic route, which activates caspase-8. The apoptotic signal is amplified by this route, which effectively kills tumor cells. It has been demonstrated that ellagic acid, one of the main polyphenols in pomegranates, is essential to this process.[33]

Inhibition of Angiogenesis:

Tumor growth and metastasis depend on angiogenesis, the creation of new blood vessels. By specifically targeting vascular endothelial growth factor (VEGF), a crucial regulator of angiogenesis, pomegranate polyphenols demonstrate potent anti-angiogenic actions. The main ellagitannins in pomegranates, punicalagins, inhibit the expression of VEGF and the signaling pathways that are linked to it, including mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K)/Akt.[34] Pomegranate chemicals also make matrix metalloproteinases (MMPs) less active, especially MMP-2 and MMP-9, which are important enzymes for the breakdown of the extracellular matrix during angiogenesis. The migration and invasion of endothelial cells necessary for the creation of new blood vessels are inhibited by this inhibition. Pomegranate extracts dramatically lower microvessel density, which is associated with limited tumor growth, according to studies conducted using in vivo tumor models.[35]

Anti-inflammatory Effects:

One known factor contributing to the development, spread, and metastasis of cancer is chronic inflammation. Pomegranate polyphenols target important inflammatory mediators to produce potent anti-inflammatory actions. They decrease the synthesis of pro-inflammatory cytokines such tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) by blocking the nuclear factor-kappa B (NF-κB) pathway, a master regulator of inflammation.[36] Pomegranate also inhibits the activity of two enzymes that contribute to the inflammatory tumor microenvironment: cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). In addition to lowering the risk of cancer, lowering these inflammatory markers also makes the environment less conducive to the growth and spread of tumors.[37]

Combination Therapies and Synergistic Effects:
The anti-inflammatory and anti-angiogenic qualities of pomegranates increase their effectiveness when combined with other natural remedies like curcumin or traditional treatments. For example, research has demonstrated that curcumin and pomegranate extracts together considerably increase apoptosis and decrease angiogenesis more successfully than either substance alone, offering a viable approach to integrative cancer treatment.[38]

Safety and Clinical Relevance:
Preclinical and clinical research have shown no notable side effects, indicating that pomegranate extracts are generally well tolerated. Their promise as a supplemental therapy in cancer care is highlighted by their low toxicity and capacity to target several cancer-promoting pathways.[39]

2.2 Turmeric

Cell Cycle Arrest:
Curcumin has a major impact on controlling the cell cycle, which is a crucial step in the growth of cancer cells. Curcumin causes cell cycle arrest at crucial stages including G1/S and G2/M by targeting several checkpoints. Cyclins and cyclin-dependent kinases (CDKs), such as cyclin D1 and CDK4, which are overexpressed in many malignancies, are downregulated to achieve this effect. Furthermore, curcumin inhibits the growth of cancer cells by increasing the expression of cyclin-dependent kinase inhibitors (CKIs) such p21 and p27. Numerous cancer types, including lung, colon, and breast malignancies, have shown these effects.[40]

Inhibition of Metastasis:
Curcumin successfully prevents metastasis, which is the process by which cancer spreads to other organs. The main way to accomplish this is by suppressing matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, which break down the extracellular matrix and promote the invasion of cancer cells. Furthermore, by altering important regulators like vimentin and E-cadherin, curcumin inhibits the epithelial-to-mesenchymal transition (EMT), a crucial stage in metastasis. By focusing on these pathways, curcumin has shown a notable decrease in the potential for metastasis in models of prostate cancer.[41]

Modulation of Signaling Pathways:
Curcumin is a powerful anticancer drug because of its capacity to alter several signaling pathways.

1. **Nuclear Factor-kappa B (NF-κB)**: Curcumin prevents NF-κB, a transcription factor implicated in inflammation, cancer cell survival, and treatment resistance, from being activated. Curcumin inhibits NF-κB, which in turn lowers the expression of genes like VEGF and Bcl-2 that are linked to angiogenesis, cell proliferation, and anti-apoptosis.[42]
2. **Signal Transducer and Activator of Transcription 3 (STAT3)**: STAT3 encourages tumor development and metastasis and is commonly activated in malignancies. By blocking upstream kinases like Janus kinases (JAKs), curcumin inhibits STAT3 activation and lowers the expression of downstream targets including survivin and cyclin D1.[43]
3. **Phosphoinositide 3-Kinase/Akt (PI3K/Akt)**: Curcumin inhibits the PI3K/Akt pathway, which promotes cell growth and survival and is frequently overactivated in malignancies. Curcumin reduces cell growth and encourages apoptosis via altering this mechanism.[44]

Synergistic Effects with Conventional Therapies
By sensitizing cancer cells and overcoming drug resistance, curcumin has been demonstrated to improve the effectiveness of traditional cancer treatments, such as chemotherapy and radiation therapy. Curcumin, for example, increases the effectiveness of paclitaxel and cisplatin while lowering dosages and decreasing adverse effects. It is a desirable option for combination therapy because to its capacity to affect several pathways at once.[45]

Bioavailability and Delivery Systems
Curcumin's low bioavailability restricts its clinical use despite its broad anticancer potential. Techniques to improve its stability, absorption, and systemic retention have been devised, including the use of liposomes, nanoparticles, and curcumin analogs. For instance, preclinical research has demonstrated that curcumin-loaded nanoparticles exhibit better anticancer effects than free curcumin.[46]

Synergistic Effects of Pomegranate and Turmeric:

Enhanced Bioavailability:
Curcumin's limited bioavailability is one of its main drawbacks as a medicinal drug, impeding its clinical effectiveness. It has been demonstrated that pomegranates, which are high in polyphenols such punicalagins

and ellagic acid, improve the absorption and bioavailability of other bioactive substances. Research indicates that pomegranate and curcumin co-administration may enhance the therapeutic effects of curcumin by improving intestinal absorption and stability.[47]

Pomegranate polyphenols have the ability to mechanistically block metabolic enzymes that are important in the quick digestion and clearance of curcumin, including cytochrome P450 and glucuronidases. Curcumin's breakdown is slowed by this inhibition, extending its time in the systemic circulation. Additionally, curcumin's conversion into its active metabolites, such tetrahydrocurcumin, which have potent anticancer activities, can be facilitated by pomegranates' capacity to modify the composition of the gut microbiota.[48]

Complementary Mechanisms of Action:

By utilizing their different but complimentary modes of action, pomegranate and curcumin together provide a comprehensive strategy to cancer treatment:

1. **Apoptosis Induction** Pomegranate increases mitochondrial-mediated apoptosis by modifying Bcl-2 family proteins, whereas curcumin stimulates caspase-mediated apoptotic pathways. When combined, they increase the cancer cells' apoptotic response.[49]
2. **Anti-inflammatory Effects**: While pomegranate reduces COX-2 and iNOS activity, curcumin inhibits the NF-κB signaling pathway, lowering the generation of inflammatory cytokines. A less conducive environment for the spread of cancer is produced by this combined targeting of inflammatory pathways.[50]
3. **Angiogenesis Inhibition**: Pomegranate and curcumin both suppress angiogenesis by lowering MMP activity and VEGF expression. The vascularization required for tumor growth and metastasis may be further suppressed by their combination.[51]
4. **Oxidative Stress Reduction**: Curcumin's capacity to neutralize reactive oxygen species (ROS) is enhanced by the antioxidant polyphenols found in pomegranates, which shield cells from DNA damage and lower the risk of cancer.[52]

Preclinical and Clinical Evidence:

According to preclinical research, the anticancer activity of curcumin and pomegranate extract is increased when compared to when either substance is used alone. In models of prostate cancer, for example, the combination considerably decreased tumor volume compared to solo therapies. Likewise, the combination led to increased rates of cell cycle arrest and apoptosis in breast cancer cell lines.[53] Prostate-specific antigen (PSA) levels in patients with prostate cancer have been found to decrease in clinical trials examining polyphenol-rich formulations, such as curcumin and pomegranate, suggesting possible advantages in slowing the progression of the illness.[54]

Safety and Tolerability:

Pomegranate and curcumin work well together, and preclinical and clinical research have shown few negative side effects. Due to their low toxicity and natural origin, these substances are good choices for long-term application in integrative cancer treatment.[55]

5. Toxicity and Safety Profile:

5.1 Pomegranate:

Safety Profile:

Since pomegranates are generally accepted to be safe for human consumption, people all over the world eat their juice, seeds, and extracts as part of their diets or as supplements. Its use in preclinical and clinical contexts has been linked to few negative effects, according to studies. Mild gastrointestinal problems like nausea, bloating, and diarrhea are often reported side effects, when they occur, and they are usually dose-dependent.[56] Additionally, even at comparatively high dosages, pomegranate extracts do not exhibit any notable harmful consequences. Pomegranate juice's safety in regular dietary usage was confirmed by a study on healthy people who drank it every day for extended periods of time. The study found no clinically significant abnormalities in liver or kidney function tests.[57]

Potential Drug Interactions:

The possibility of pomegranate interactions with specific medications is one factor to take into account when evaluating its safety. Pomegranate juice, like grapefruit, has the potential to block cytochrome P450 enzymes, especially CYP3A4, which are involved in the metabolism of numerous medications. This combination may raise the plasma levels of medications such as warfarin or statins, which could have negative effects. Before adding pomegranate extracts to a long-term treatment regimen, patients should speak with their doctors.[58]

Long-term Safety:

Pomegranate consumption in food is thought to be safe, but the long-term safety of concentrated extracts is still up for debate. Concentrated versions feature far higher concentrations of active ingredients like punicalagins and ellagic acid, which may cause unexpected side effects after extended use.[59] High-dose pomegranate extracts have not been demonstrated to be carcinogenic or genotoxic in preclinical research. However, additional research is necessary to rule out cumulative effects or interactions with chronic conditions when using this product for an extended period of time in humans. It is also crucial to conduct clinical trials to assess the extracts' long-term safety in populations with chronic illnesses like cancer or cardiovascular conditions.[60]

Special Populations:

Most people, especially the elderly and those with comorbidities, tolerate pomegranate extracts well. However, because there is a lack of information regarding safety in these categories, women who are pregnant or nursing should exercise caution.[61]

5.2 Turmeric:

Safety Profile:

Turmeric's key ingredient, curcumin, has been used for millennia in traditional medicine and is thought to be safe to eat. According to the U.S. Food and Drug Administration (FDA), curcumin is "Generally Recognized as Safe" (GRAS). Even at dosages as high as 12 grams daily, clinical trials have shown little side effects, indicating its broad safety margin.[62] Curcumin has very few adverse effects, such as mild gastrointestinal symptoms like nausea, flatulence, or diarrhea, when taken at normal dietary levels. At greater dosages, these effects are more frequently seen.[63] Although long-term studies on curcumin supplementation have not revealed any serious toxicological issues, more investigation is required to completely comprehend its safety profile in particular groups, such as women who are pregnant or nursing.[64]

Bioavailability Issues:

Curcumin's poor bioavailability severely restricts its clinical use, despite its encouraging therapeutic promise. This problem results from a number of factors:

1. **Low Solubility**: Because curcumin is poorly soluble in water, the gastrointestinal tract absorbs it less readily.
2. **Rapid Metabolism**: Curcumin is rapidly broken down in the intestinal wall and liver after absorption, mostly into less bioactive glucuronides and sulfates.
3. **Rapid Systemic Elimination**: Curcumin has low systemic concentrations because it is quickly eliminated from the body.[65]

Strategies to Enhance Bioavailability

Several tactics have been devised to increase curcumin's bioavailability in order to get over these restrictions:

1. **Use of Adjuvants**: It has been demonstrated that piperine, a substance present in black pepper, increases the absorption of curcumin by 2000% by blocking its metabolism.[66]
2. **Liposomal Curcumin**: Curcumin's solubility and stability are improved by encapsulation in liposomes, which also improves absorption and systemic retention.[67]
3. **Nanoparticle Formulations**: Higher bioavailability is the result of curcumin nanoparticles' increased surface area and solubility. In preclinical animals, these formulations have shown improved antitumor efficacy.[68]
4. **Curcumin-Phospholipid Complexes**: Complexation with phospholipids, like in "Meriva," increases the bioavailability and therapeutic effectiveness of curcumin.[69]

Clinical Implications:

Better therapeutic results are directly correlated with increased bioavailability. For example, in preclinical and clinical trials, curcumin formulations with improved absorption have shown greater anticancer, anti-inflammatory, and antioxidant benefits.[70]

5.3 Combined use:

General Safety of Combined Use:

According to recent research, pomegranate and turmeric together seem to be safe, as each of these natural compounds has a proven safety record. As was previously mentioned, curcumin, the active ingredient in turmeric, has also been found to be safe in preclinical and clinical settings, while pomegranates are widely thought to be safe to eat with few documented adverse effects. When taken in the recommended dosages, the synergistic combination of these two bioactive substances does not seem to have any notable negative effects

or toxicity.[71] However, little study has been done on the combined use of curcumin and pomegranate, especially at higher doses or in concentrated forms, despite the fact that their separate safety profiles are well-established. Pomegranate and curcumin together have demonstrated increased anticancer activity in preclinical research without appreciable toxicity; however, these findings have not been thoroughly validated in human trials.[72]

Potential Drug Interactions:

When pomegranate and turmeric (more especially, curcumin) are taken with traditional cancer treatments, it may be necessary to take into account the possibility of drug interactions. It is well known that pomegranate inhibits cytochrome P450 enzymes, especially CYP3A4, which is essential for the metabolism of several drugs, including some chemotherapy ones. This might change these medications' pharmacokinetics and result in drug interactions.[73] Similar characteristics are also exhibited by curcumin, which inhibits drug metabolism by influencing several enzymes involved in phase I and phase II drug metabolism. Theoretically, pomegranate and curcumin together could intensify these effects, changing the toxicity or efficacy of medications in people receiving chemotherapy or other pharmaceutical therapies.[74]

Long-term Safety and Cancer Therapy:

Long-term research is still required, particularly when it comes to cancer patients receiving traditional treatments, even if short-term safety data indicates that using pomegranate and turmeric together is safe. Natural substances like pomegranate and curcumin may interact with the various drugs that cancer patients are frequently prescribed, such as immunotherapies, targeted treatments, and chemotherapy. To ensure there are no unfavorable interactions or diminished therapeutic efficacy, more research is required to evaluate the long-term impact and safety of combining these natural medicines with traditional cancer treatments.[75] Furthermore, as these substances can affect drug metabolism and organ function, thorough research is needed to determine the long-term safety of concentrated extracts or supplements (such as pomegranate extract or curcumin formulations) in cancer patients.[76]

6. Conclusion:

Cancer is still a major worldwide health concern, so new, safe, and effective treatment approaches must be investigated. The application of natural substances, especially turmeric (Curcuma longa) and pomegranates (Punica granatum), has drawn a lot of interest because of their rich phytochemical profiles and proven anticancer effects. With an emphasis on their safety profiles, modes of action, and potential for synergistic benefits in cancer therapy, this review has emphasized the effects of these two natural medicines both alone and in combination. The potent bioactive substances found in pomegranates, such as polyphenols, flavonoids, and tannins, give them their anti-cancer and antioxidant properties. It has been demonstrated that important components such anthocyanins and punicalagins cause apoptosis, stop cell division, and prevent angiogenesis and metastasis. Prostate and breast cancers are among the many cancer types that these systems are essential in the fight against. Similar to this, curcumin, the main active ingredient in turmeric, has anti-inflammatory, antioxidant, and anti-proliferative qualities that give it a variety of anticancer effects. Curcumin inhibits the development and spread of cancer cells by modulating a number of important signaling pathways, including as NF-κB, MAPK, and PI3K/Akt.

Pomegranate and turmeric together present a viable way to improve medicinal effectiveness. Research indicates that their complimentary modes of action may result in better cancer therapy outcomes. Pomegranate and curcumin, for example, have been demonstrated to increase apoptosis and inhibit tumor growth more efficiently when taken together than when taken alone. Evidence suggesting pomegranate may increase curcumin's bioavailability, resolving one of the major barriers to curcumin's clinical use, lends additional credence to this synergistic potential. Both curcumin and pomegranate have relatively good safety ratings, with few side effects noted in preclinical and clinical research. However, care should be taken due to possible drug interactions, especially with drugs that are processed by cytochrome P450 enzymes. Although both substances are well tolerated, it is still unclear if using them together will be safe in the long run, particularly for cancer patients receiving traditional treatments. Clinical trials should be the main focus of future research to confirm the combination's safety and effectiveness, especially in a variety of patient populations. Pomegranate and turmeric together offer a promising approach to cancer treatment, utilizing both their individual and complementary benefits to improve treatment results while reducing toxicity. More research into the mechanisms, safety, and clinical uses of these natural substances will be crucial as integrative oncology develops. We can open the door to more comprehensive and successful treatment plans

that enhance patient quality of life and therapeutic outcomes by comprehending their possible roles in cancer care.

7. Abbrevations:

COX-2: Cyclooxygenase-2, **EMT**: Epithelial-to-Mesenchymal Transition, **FDA**: U.S. Food and Drug Administration, **IL**: Interleukin, **iNOS**: Inducible Nitric Oxide Synthase, **MAPK**: Mitogen-Activated Protein Kinase, **MMP**: Matrix Metalloproteinase, **NF-κB**: Nuclear Factor-kappa B, **PI3K/Akt**: Phosphoinositide 3-Kinase/Akt, **PSA**: Prostate-Specific Antigen, **ROS**: Reactive Oxygen Species, **SOD**: Superoxide Dismutase, **TIMP**: Tissue Inhibitors of Metalloproteinases, **TNF-α**: Tumor Necrosis Factor-alpha, **Urolithins**: Metabolites derived from the gut microbiota from ellagitannins found in pomegranate, **JAKs**: Janus Kinases, **CKIs**: Cyclin-Dependent Kinase Inhibitors

8. Conflict of Interest:

None.

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