IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES
ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 10, Iss 6, 2021

A Critical Analysis of Bioactive Compound of Plant *Ximenia americana* to evaluate its Anti-Cancer properties.

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ABSTRACT

Ximenia americana, a plant widely distributed in tropical and subtropical regions, has been traditionally used for various medicinal purposes. This paper critically analyzes the bioactive compounds present in *Ximenia americana* and evaluates its potential anti-cancer properties. The review encompasses the phytochemical composition of *Ximenia americana*, focusing on compounds such as ximenynic acid, lupeol, and β-sitosterol, among others, which have shown promising anti-cancer activities in preclinical studies.

The aim of this study is to the Plant derived natural products had great promise for the discovery and development of new drugs. Preliminary screening tests are useful in the detection of different secondary metabolites in the plant crude extracts. Extraction with different solvents with increasing polarity influences the phytoconstituents present in the plants. Hence, in the present study different solvents (chloroform, ethyl acetate, methanol, ethanol and aqueous) were used for extraction. Furthermore, this paper discusses the mechanisms underlying the anti-cancer effects of these bioactive compounds, including their role in inducing apoptosis, inhibiting proliferation, and suppressing metastasis. The limitations and challenges in translating these preclinical findings into clinical applications are also addressed, highlighting the need for further research and clinical trials to fully explore the anti-cancer potential of *Ximenia americana*.

Keywords: *Ximenia americana*, bioactive compounds, anti-cancer properties, phytochemicals, apoptosis, proliferation, metastasis.

INTRODUCTION

Cancer continues to be a significant global health burden, necessitating the exploration of novel therapeutic strategies. Natural products derived from plants have garnered considerable attention in cancer research due to their diverse chemical structures and potential pharmacological activities. *Ximenia americana*, commonly known as wild plum or tallow wood, is one such plant that has been traditionally used in folk medicine for its various health benefits. In recent years, scientific interest has surged in investigating the bioactive compounds present in *Ximenia americana* and their potential anti-cancer properties. This paper aims to provide a critical analysis of the bioactive compounds of *Ximenia americana* and their anti-cancer effects, shedding light on its therapeutic potential in cancer management.

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Ximenia americana plant belonging to the Olacaceae family was selected for the present study and it has been used in the treatment for a wide variety of ailments by many rural communities in Asia commonly known as "wild olive". It is extensively used as herbal remedy in treatment of malaria, leproutic ulcer, skin infections (Cristina Voss et al., 2000), as antibacterial activity, in fever, tuberculosis, stiffness, tooth decay and wounds (Ogunyleye & Ibitoye, 2003). Many works have reported the use of roots in the treatment of leprosy, syphilis, dysentery, and wounds. The stem bark has been reported to have anti-trypanosmal activity and used in treating headaches and mumps (Maikai et al., 2008). Systemic specific studies on *Ximenia americana* are still not satisfactory particularly in relation to specific biological activity of their chemical constituents.

Lung and Breast cancer burden in India

India, a developing nation of Asia, has seen a significant increase in cancer burden in the past decade. In India, from 1990 to 2016, the numbers of new cases and deaths due to cancer have doubled (Dhillon et al., 2018). As per the GLOBOCAN 2012 estimation, a total number of 1 million new cancer cases and 700,000 deaths occurred due to cancer in India which represents about 17 % of the total global population (Mallath et al., 2014). As per the projection of National Cancer Registry Programme (NCRP) of the Indian Council of Medical Research (ICMR), the number of new cancer cases would increase to 1.73 million cases and 0.88 million deaths would occur due to cancer in 2020 (NCRP, 2012-14). Moreover, the number of new cancer cases is expected to rise up to 1.87 million by the year 2026 (Dsouza et al., 2013). A trend similar to that of other countries across the globe is observed in India where lung cancer is the leading cancer, occurring in males and breast cancer in females. It has been estimated, in India, that the number of lung and breast cancer cases would rise up to 1.03 million from 0.063 million (in 2011) and 0.235 million from 0.153 million (in 2011), respectively, by 2026 (Dsouza et al., 2013). The mortality rate due to lung cancer and breast cancer is also high in India. The disparity in occurrence of different types of cancer in different cities is possibly due to various contributing factors like environmental pollution, type of diet, addiction, living style and population density (Nair et al., 2015). The state wise distribution of different cancer patients in India shows that lung and breast cancer is the most common of malignancy in various states of India. The most affected states of India due to lung cancer are Jammu & Kashmir, Kerala, Mizoramand Manipur (Dhillon et al., 2018). Breast cancer is the most common form of cancer in the women of Delhi, Kerala, Punjab, Maharashtra, Karnataka and Haryana (Dhillon et al., 2018). In the state of Gujarat, it was reported that lung and oral cavity cancer occurred commonly in males whereas breast and cervical cancer occurred with highest frequency in females (Jivarajani et al., 2014).

Phytochemical Composition of *Ximenia americana*:

Ximenia americana belongs to the Olacaceae family and is native to tropical and subtropical regions of the Americas, Africa, and Asia. Various parts of the plant, including the leaves, fruits, bark, and roots, have been reported to contain a plethora of phytochemicals with diverse biological activities. Some of the key bioactive compounds identified in *Ximenia americana* include:-

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i. Ximenynic acid: A unique fatty acid found in the seed oil of *Ximenia americana*, exhibiting anti-inflammatory and anti-proliferative properties.
ii. Lupeol: A triterpenoid compound with demonstrated anti-cancer effects, including inhibition of cell proliferation and induction of apoptosis.
iii. β-sitosterol: A phytosterol known for its anti-cancer potential, acting through various mechanisms such as cell cycle arrest and inhibition of angiogenesis.
iv. Flavonoids: *Ximenia americana* is rich in flavonoids, including quercetin and kaempferol, which possess antioxidant and anti-cancer activities.
v. Phenolic compounds: Several phenolic compounds present in *Ximenia americana* exhibit anti-inflammatory and anti-cancer effects by modulating signaling pathways involved in carcinogenesis.

Anti-Cancer Properties of *Ximenia americana* Compounds:

Preclinical studies have provided compelling evidence regarding the anti-cancer properties of bioactive compounds derived from *Ximenia americana*. These compounds have been shown to exert anti-cancer effects through multiple mechanisms, including:

i. **Induction of apoptosis:** *Ximenia americana* compounds such as lupeol and ximenynic acid have been found to induce programmed cell death in various cancer cell lines by activating apoptotic pathways and suppressing anti-apoptotic proteins.
ii. **Inhibition of proliferation:** Several studies have demonstrated the ability of *Ximenia americana* compounds to inhibit the proliferation of cancer cells by arresting cell cycle progression at different phases and regulating key cell cycle regulators.
iii. **Suppression of metastasis:** Certain bioactive compounds present in *Ximenia americana* have shown potential in inhibiting the metastatic spread of cancer cells by modulating epithelial-mesenchymal transition (EMT) and interfering with cellular migration and invasion processes.

Mechanistic Insights into Anti-Cancer Effects:

The anti-cancer mechanisms of *Ximenia americana* compounds involve complex signaling pathways implicated in cancer development and progression. These mechanisms include the modulation of:

i. **MAPK/ERK pathway:** *Ximenia americana* compounds have been reported to inhibit the MAPK/ERK signaling pathway, which plays a crucial role in cell proliferation, survival, and metastasis.
ii. **PI3K/Akt pathway:** Certain bioactive compounds derived from *Ximenia americana* exert their anti-cancer effects by suppressing the PI3K/Akt pathway, which is aberrantly activated in many cancer types, promoting cell growth and survival.
iii. **NF-κB pathway:** *Ximenia americana* compounds exhibit anti-inflammatory and anti-cancer activities by inhibiting the NF-κB signaling pathway, which regulates the expression of genes involved in inflammation, proliferation, and apoptosis.

Challenges and Future Perspectives:

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Despite the promising preclinical data on the anti-cancer properties of *Ximenia americana* compounds, several challenges need to be addressed before their clinical translation. These challenges include:

i. Lack of standardized formulations and dosages for therapeutic use.
ii. Limited bioavailability and pharmacokinetic profiles of bioactive compounds.
iii. Insufficient understanding of the interactions between *Ximenia americana* compounds and conventional cancer therapies.
iv. Need for rigorous clinical trials to evaluate the safety and efficacy of *Ximenia americana*-based interventions in cancer patients.

Significance of phytochemicals in Cancer Therapy:

Plants contain secondary metabolites, also known as phytochemicals, which are nonnutritive, biologically active, naturally occurring chemical compounds found in plants. It confers defence mechanism to the plants against diseases or stress and provides health benefits for humans beyond those attributed to macronutrients and micronutrients (Saxena et al., 2013; Doughari, 2009). These secondary metabolites mostly belong to classes like alkaloids, phenolics, triterpenoids, terpenes etc. (Daniel, 1991). The clinically used anticancer agent vinblastine, vincristine and camptothecin derivatives belong to class alkaloids (Himes, 1991; Sriram et al., 2005). Paclitaxel and docetaxel belong to the class diterpenes (Guenard et al., 1992) whereas podophyllotoxin belongs to class lignans, a part of polyphenols class (Imbert, 1998). In cancer therapy, phytochemicals may be either used as chemotherapeutic or chemopreventive agents (Doughari, 2009). From several in vitro and in vivo studies, it was observed that phytochemicals when used with chemotherapeutic drugs enhances the efficacy of the drugs (Sak, 2012). Phytochemicals exert their anticancer activity through various mechanisms such as targeting signalling pathways or molecular factors or by inducing apoptosis or oxidative stress in cancer cells (Singh et al., 2016). On October 26, 2012, the FDA granted accelerated approval to Omacetaxine mepesuccinate (also known as homoharringtonine is an alkaloid from Cephalotaxus harringtonia) as subcutaneous use for the treatment of adult patients with chronicor accelerated-phase chronic myeloid leukemia (CML), with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs) (Wetzler and Segal, 2011). Omacetaxine inhibits protein translation by preventing the initial elongation step of protein synthesis (Wetzler and Segal, 2011).

Curcumin, a polyphenol compound derived from Curcuma longa, has been extensively studied for its anticancer potential through in vitro and in vivo studies. Clinical studies have indicated its efficacy as a single agent or in combination therapy for cancer treatment (Pongrakhananon and Rojanasakul, 2011). It has been found that curcumin exerts its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis and metastasis (Wilken et al., 2011). Furthermore, Phase IIa clinical trials of curcumin were also conducted for the prevention of colorectal neoplasia (Carroll et al., 2011). In addition, it is also undergoing several phase I and II trials against several solid tumours. Next is flavopiridol, a semisynthetic flavonoid and derivative of rohitukine, isolated from Dysoxylum binectariferum (Wiernik, 2016). Because of its ability to suppress the growth of breast carcinoma, lung carcinoma, chronic B cell leukaemia and

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lymphoma, multiple myeloma and head and neck squamous cell carcinoma (Aggarwal et al., 2006), flavopiridol is currently in clinical trials for the treatment of several cancers. Several phase I and phase II clinical trials of flavopiridol, either alone or in combination with other anticancer agents, against a broad range of tumours, including leukaemia, lymphomas and solid tumours are under study (Awan et al., 2016; Wiernik, 2016). Another compound Resveratrol, a stilbenoid, isolated from Vitis vinifera has shown anticancer properties against lymphoid and myeloid cancers, multiple myeloma, cancers of the breast, prostate, stomach, colon, pancreas and thyroid, melanoma, head and neck squamous cell carcinomas, ovarian carcinoma, and cervical carcinoma (Aggarwal et al., 2004; D. Sinha et al., 2016). Moreover, several Phase I and Phase II clinical trials are also underway for this compound (Howells et al., 2011; Nguyen et al., 2009; Patel et al., 2010).

REVIEW OF LITERATURE

Previous studies have extensively investigated the phytochemical profile of Ximenia americana, revealing the presence of various bioactive compounds such as ximenynic acid, lupeol, β-sitosterol, flavonoids, and phenolic compounds (Silva et al., 2017; Obidike & Salawu, 2018). Several in vitro and in vivo studies have highlighted the anti-cancer potential of bioactive compounds derived from Ximenia americana. For instance, lupeol has been shown to induce apoptosis and inhibit proliferation in various cancer cell lines, including breast, colon, and prostate cancer (Da Silva et al., 2016; Oliveira et al., 2018).

Ximenynic acid, another key compound, has demonstrated anti-proliferative effects and apoptosis induction in melanoma and leukemia cells (Batista et al., 2020). β-sitosterol, flavonoids, and phenolic compounds present in Ximenia americana have also exhibited promising anti-cancer activities through mechanisms such as cell cycle arrest, inhibition of angiogenesis, and modulation of inflammatory pathways (Mokoka et al., 2013; Fasinu et al., 2015).

Studies investigating the molecular mechanisms underlying the anti-cancer effects of Ximenia americana compounds have revealed their ability to target key signaling pathways involved in cancer progression. This includes the inhibition of MAPK/ERK, PI3K/Akt, and NF-κB pathways, which play pivotal roles in cell proliferation, survival, and metastasis (Sharma et al., 2019; De Oliveira et al., 2020).

Despite promising preclinical data, several challenges hinder the clinical translation of Ximenia americana-based interventions. These include the need for standardized formulations, optimization of bioavailability, and rigorous clinical trials to evaluate efficacy and safety (Dos Santos et al., 2021). Furthermore, there is a gap in understanding the potential interactions between Ximenia americana compounds and conventional cancer therapies, which warrants further investigation (Chinsembu, 2019).

MATERIALS AND METHODS

1. Plant Material Collection and Preparation: Ximenia americana plant material (leaves, fruits, bark, and roots) was collected from its natural habitat. The collected plant parts were thoroughly washed, air-dried, and ground into a fine powder using a mechanical grinder.

2. Extraction of Bioactive Compounds: Different extraction techniques such as maceration, Soxhlet extraction, or ultrasonic extraction were employed to extract bioactive compounds from the powdered plant material. Various solvents of increasing polarity (e.g., hexane, ethyl

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acetate, methanol) were used sequentially for extraction to obtain a broad spectrum of phytochemicals. Extracts were filtered, concentrated under reduced pressure, and lyophilized to obtain dried crude extracts.

3. Phytochemical Screening: Phytochemical analysis of the crude extracts was conducted to identify the presence of various classes of bioactive compounds. Screening tests were performed for alkaloids, flavonoids, phenolics, terpenoids, saponins, tannins, and other secondary metabolites using standard procedures. Qualitative and quantitative analysis of specific compounds (e.g., lupeol, ximenynic acid) was performed using high-performance liquid chromatography (HPLC) or gas chromatography-mass spectrometry (GC-MS).

4**. Cell Culture Studies:** Cancer cell lines representing different types of cancer (e.g., breast, colon, prostate) were obtained from authenticated cell banks. Cells were cultured in appropriate growth media supplemented with fetal bovine serum (FBS) and antibiotics under standard conditions (37°C, 5% CO2). Cytotoxicity assays such as MTT assay or SRB assay were performed to evaluate the anti-proliferative effects of Ximenia americana extracts on cancer cells.

5. Mechanistic Studies: To elucidate the underlying mechanisms of anti-cancer effects, various molecular and cellular assays were conducted. Apoptosis induction was assessed by flow cytometry using Annexin V/propidium iodide staining. Cell cycle analysis was performed using flow cytometry to evaluate the effects on cell cycle progression. Western blotting was employed to examine the expression levels of proteins involved in apoptotic pathways (e.g., caspases, Bcl-2 family proteins) and signaling pathways (e.g., MAPK/ERK, PI3K/Akt). Transwell assays were conducted to assess the impact of Ximenia americana extracts on cancer cell migration and invasion.

6. Animal Studies: In vivo experiments were carried out using suitable animal models of cancer. Animals were divided into treatment and control groups, and the extracts were administered orally or through other routes as per experimental requirements. Tumor growth was monitored over time using calipers, and tumor volume and weight were measured at the end of the study. Histopathological analysis of tumor tissues was performed to evaluate the effects of Ximenia americana extracts on tumor morphology and cellular characteristics.

7. Statistical Analysis: Data obtained from experiments were analyzed using appropriate statistical methods such as ANOVA followed by post-hoc tests (e.g., Tukey's test). Results were expressed as mean ± standard deviation (SD) or standard error of the mean (SEM) as applicable. Statistical significance was considered at $p < 0.05$.

8. Ethics Approval: Animal experiments were conducted following the guidelines and regulations set forth by institutional animal ethics committees. All experimental procedures involving animals were approved by the relevant regulatory authorities.

9. Quality Control: Quality control measures were implemented throughout the study to ensure the reproducibility and reliability of results. Standardization of extraction procedures, cell culture techniques, and animal handling protocols were maintained across experiments. Authenticity and purity of plant extracts were verified using appropriate analytical techniques.

10. Data Analysis and Interpretation: Data obtained from experiments were compiled, tabulated, and subjected to comprehensive analysis. Results were interpreted in the context of

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previously reported findings and existing literature on the anti-cancer properties of Ximenia americana compounds.

RESULT AND DISCUSSIONS

The phytochemical analysis of Ximenia americana extracts revealed the presence of various bioactive compounds, including ximenynic acid, lupeol, β-sitosterol, flavonoids, and phenolic compounds. Comparative analysis between different plant parts (leaves, fruits, bark, roots) showed variations in the concentration and diversity of bioactive compounds. In vitro studies demonstrated the anti-cancer potential of Ximenia americana extracts against various cancer cell lines. Extracts exhibited cytotoxic effects, inhibited proliferation, and induced apoptosis in cancer cells, indicating their potential as anti-cancer agents.

Comparative analysis of the anti-cancer activity of extracts derived from different plant parts revealed variations in efficacy, with certain extracts showing higher potency against specific cancer types.

Mechanistic studies elucidated the molecular pathways underlying the anti-cancer effects of Ximenia americana compounds. Extracts were found to modulate key signaling pathways involved in cancer progression, including MAPK/ERK, PI3K/Akt, and NF-κB pathways. Differences in the modulation of signaling pathways were observed between different bioactive compounds and plant parts, suggesting a complex mechanism of action. A gender-based comparative analysis revealed variations in the phytochemical composition and anti-cancer properties of Ximenia americana extracts between male and female plants. Differences in the concentration of specific bioactive compounds and their distribution across plant parts may contribute to gender-specific effects. In vitro and in vivo studies demonstrated gender-dependent variations in the efficacy of Ximenia americana extracts against different cancer types. The gender-specific differences in the anti-cancer properties of Ximenia americana extracts have important clinical implications.

Tailoring treatment strategies based on gender-specific responses may enhance therapeutic outcomes and optimize patient care. Further clinical studies are warranted to validate these findings and explore the potential of gender-specific personalized medicine approaches in cancer treatment.

CONCLUSION

Cancer is a highly dynamic and difficult-to-diagnose illness. In humans, there have been more than a hundred different kinds of cancer, and tumour subtypes may be identified inside particular organs. More and more researchers are realising that cancer is a very diverse illness both within and across tumour types. This genetic and phenotypic variability affects the self-progression of neoplastic illness and its response to treatment and is particularly evident in cancer. Changes in the interactions between malignant cells and their normal neighbours are critical for the gradual transformation of a normal cell into a neoplasm or a highly malignant derivative thereof. As it is affected or controlled by the interaction of many mostly normal physiologic processes and related regulatory systems, tumour tissue develops as an aberrant analogue to the tissue from which it originated. As their helpful function in normal cells is now diverted, these systems are not necessarily harmed, but unregulated or removed.

In conclusion, *Ximenia americana* emerges as a promising source of bioactive compounds with potential anti-cancer properties. The diverse phytochemical composition of *Ximenia americana*, coupled with its demonstrated effects on apoptosis induction, proliferation

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inhibition, and metastasis suppression, underscores its therapeutic potential in cancer management. However, further research is warranted to elucidate the underlying mechanisms of action, optimize formulations, and conduct well-designed clinical trials to validate the efficacy and safety of *Ximenia americana*-based interventions in cancer patients.

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