***Review Article***

# "The Pharmacological Properties of Cola nitida Phytochemicals: Implications for Cancer Therapy Development"


## Abstract

Cancer continues to be the leading cause of mortality worldwide, despite significant attempts to identify new risk factors, create earlier diagnostic indicators, and investigate alternative therapy options. This rising burden of cancer worldwide results in the advancement of innovative methods of cancer prevention and treatment leading to the developed idea of cancer chemoprevention, with an emphasis on employing natural substances included in the diet to inhibit tumor development. Newer techniques like immunotherapy and gene therapy are used in addition to conventional cancer therapies including radiation, chemotherapy, and surgery. Nonetheless, the potential of natural substances needs to be exploited. Natural products which can be proteins, carbohydrates, or nucleic acids in their forms or conjugated have tendencies to trigger innate and adaptive immunity, infusion reactions, inflammatory responses, hypersensitivity reactions, and other immunological responses. Numerous bioactive substances found in Cola nitida, such as flavonoids, catechin, flavonoids, tannins, alkaloids, and phenolics, have been shown to have promising medicinal qualities, such as the ability to prevent cancer, function as antioxidants, and stop the proliferation of cancer cells using some of the immunological mechanism. This study explores the molecular routes by which these bioactive chemicals cause apoptosis, inhibit angiogenesis, and modify signal transduction pathways to achieve their anticancer effects. The study concludes by highlighting the tremendous multimodal therapeutic potential of Cola nitida in the creation of safer and more effective cancer treatments.



**Keywords:** Cola nitida, anticancer, chemoprevention, phytochemical, anti-inflammatory, multimodal treatment, natural product.

## 1.0. Introduction

The concept of cancer chemoprevention has arisen as a potential strategy to combat the rising incidence of cancer worldwide [1]. It involves using natural or synthetic compounds in food to counteract, reduce, or limit the progression of tumorigenesis. Due to its rising frequency, cancer, which is defined as the unrestrained proliferation of aberrant cells in the body stands as one of the most common illnesses in the world [1,2]. Therefore, new approaches must be developed to prevent and cure this dangerous illness. According to the World Health Organization (WHO), one in five people will develop cancer at some point in their lives, and one in nine men and one in twelve women will pass away from the disease. It was also reported that there were 9.7 million deaths and an astounding 20 million cases of cancer in 2022 [3]. Lung cancer was found to be the most common cancer worldwide in 2022, accounting for 2.5 million new cases, or 12.4% of all new cases [3,4]. Closely behind were colon cancer (1.9 million cases, 9.6%), prostate cancer (1.5 million cases, 7.3%), stomach cancer (970,000 cases, 4.9%), and female breast cancer (2.3 million cases, 11.6%) [3, 5]. Surgery, chemotherapy, and radiation therapy are common methods of treating cancer. However, newer treatments like immunotherapy, stem cell therapy, and gene therapy including CAR-T cell therapy are also gaining popularity [6]. Anticancer drugs work by preventing the growth and death of malignant cells while causing the least amount of damage to healthy cells. This is accomplished by processes such as immune response activation, tumor suppression, apoptosis induction, and immune system detection of cancer cells [7, 8]. Certain naturally occurring substances, such as those originating from plants, initiate and promote these processes, controlling the growth of cancer cells via a variety of methods. The perennial plant known as Cola nitida is grown mainly for its seeds, which are eaten for their stimulating properties and are used in traditional ceremonies across West Africa [9]. Cola nitida is a member of the Sterculiaceae family and is one of the most common species of Cola. It is abundant in the tropical rainforest region of Africa and comes in over twenty variations. Its many uses include the manufacturing of beverages, stimulatory effects, and possible drug development benefits [10]. Due to its wide range of bioactive compounds, which are also known as phytochemicals and include kaolin, phenolics, alkaloids, tannins, caffeine, flavonoids, and theobromine, Cola nitida shows promising therapeutic potential in both traditional herbal medicine and contemporary research [9,10,11]. These phytochemicals are

important building blocks for the creation of several medications and are found in large quantities in the Cola nitida's seed, pod, and seed shell. However, a lot of its potential is still unrealized. Previous research has demonstrated the health benefits of Cola nitida [11]. It may have anticarcinogenic, antioxidant, antibacterial, and antidiabetic effects in addition to its capacity to prevent pituitary cells from releasing luteinizing hormones (LH), which may indicate that it has a function in reproductive regulation [12]. This study aims to explore the possible health advantages of the phytochemicals found in Cola nitida, specifically their potential as a cancer treatment intervention.

***Figure 1 showing the Cola nitida* (Available)**

## 2.0. Anticancer Essentials of Cola Nitida

An uncontrolled, aggressive neoplastic cell is created when a normal, functional cell undergoes a complex series of processes known as carcinogenesis. The beginning, promotion, and advancement phases of this process are all included, and it ends with metastasis to other organs. The main forces behind these shifts in the development of cancer are genetic and epigenetic changes [13]. On the other hand, the application of phytochemicals or nutraceuticals in oncology has shown encouraging results in terms of both disease prevention and treatment [14]. Moreover,

nutraceuticals' potential has beyond earlier boundaries; new studies have shown how they can alter the immunogenic profile of cancer cells, making them more vulnerable to immune surveillance mechanisms' destruction [14, 15]. A well-balanced diet high in fruits and vegetables is positively correlated with the prevention of crippling diseases such as cancer [15]. Polyphenols, a dietary class rich in bioactive compounds, are partially responsible for this link. Natural substances have been demonstrated to obstruct the development of cancer by several molecular mechanisms, such as cell cycle regulation, apoptosis induction, inhibition of migration and invasion, suppression of the cancer stemness phenotype, and modification of molecular signaling pathways [15, 16]. Cola nitida is a naturally occurring plant that has gained recognition for a variety of medicinal properties, one of which is its ability to treat cancer [16]. Phytochemicals are naturally occurring substances that are mostly produced by plants to strengthen their resistance to illness. Phytochemical analysis of the Cola nitida tree's leaves, bark, twigs, and nuts has revealed the presence of reducing sugars, steroids, alkaloids, tannins, flavonoids, glycosides, volatile oils, and balsams [17]. An herb with bitter-sweet and astringent characteristics, cola nitida is well-known for its heart-stimulating and antidepressant effects. It has high concentrations of phenolics including epicatechin, procyanidins, and catechin, as well as alkaloids like caffeine [18]. Because of its numerous anticancer qualities and antioxidant activities, essential antioxidant minerals (oxygen, carbon, potassium, phosphorus, and magnesium), and notable total phenolic and total flavonoid contents, Cola nitida is therefore acknowledged as an anticancer agent [19].

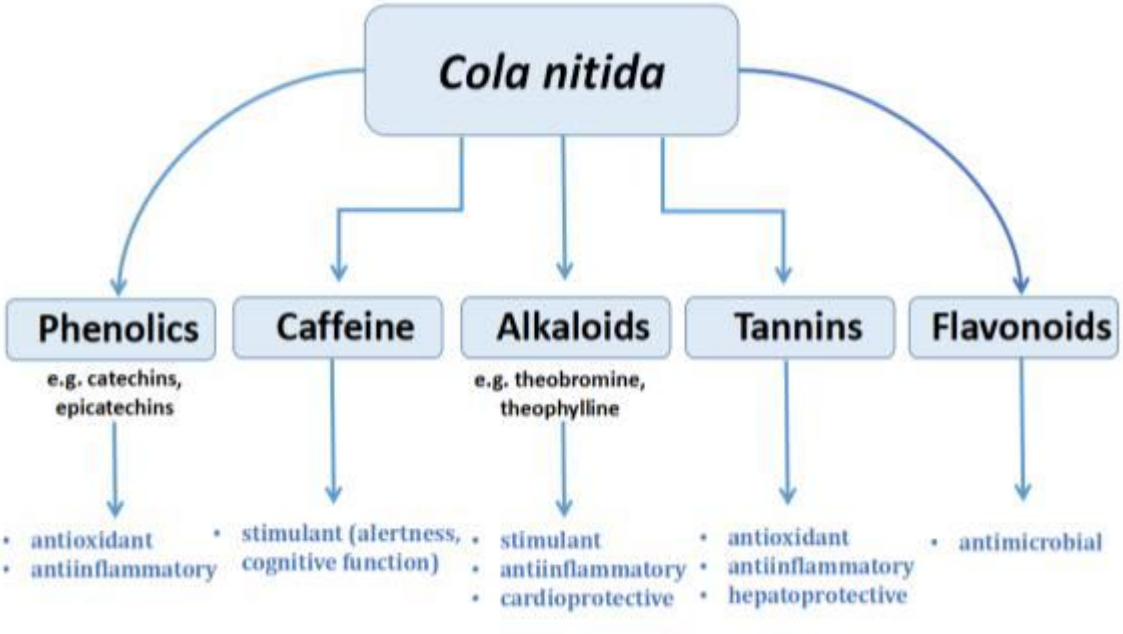


*Figure 2 showing bioactive ingredients of Cola nitidat [25].*

**3.0 Anticancer Mechanisms of Cola nitida Bioactive agents**

Current treatment practices emphasize how important it is to block critical metabolic processes that cause normal cells to become malignant [20]. The Ap-1 and NF-KB activation pathways are two of the main signal transduction pathways involved in cancer that are significantly inhibited by medicinal herbs such as Cola nitida. Studies show that NF-KB controls the expression of genes related to angiogenesis and the fast growth of cancer cells when it interacts with transcription factors like activator protein-1 (AP-1) [21]. The steroidal saponin ginsenoside, which is included in the botanical extract of mountain ginseng, inhibits the proliferation of lung cancer cells via modifying the NF-KB signaling pathway [22]. Therefore, the possession of steroidal saponins by Cola nitida might be an important trigger to use the NF-KB signaling pathway mechanism to stop carcinogenesis [23]. Moreover, cola nitida, particularly as the result of its high caffeine infusion the Cox-2 Pathway can block the prostaglandin (PG) cascade and inhibit cyclooxygenase (COX), namely COX-2. These actions may affect the angiogenesis and proliferation of cancerous cells [24]. Furthermore, Cola nitida methanol extract has demonstrated potential in reducing nociception and inflammation through the cholinergic system [25].

### 3.1 Antioxidant nature of Cola nitida

The pathogenesis of many disease states is linked to oxidative stress and compromised antioxidant systems, highlighting the critical role antioxidants play in squelching oxidative stress. An imbalance in the body's ability to neutralize or detoxify free radicals by neutralizing their detrimental effects through antioxidant synthesis leads to oxidative stress [26]. The body produces free radicals as a result of normal metabolic processes and exposure to adverse pathophysiological conditions. Through a variety of methods, these unstable entities can cause injury to cells [26, 27]. Free radicals have been linked to aging and several human diseases because they can harmfully alter lipids, proteins, and DNA [28]. However, the damage they cause to DNA is the most serious effect because it is directly related to the onset of cancer. Plant-based antioxidants function by scavenging free radicals, protecting against the harmful effects of reactive oxygen species, and providing defense against common ailments including inflammation [29]. A therapeutic strategy for the treatment of prostatic cancer might be derived from this inhibition by using LHRH agonists to desensitize the pituitary gland, which would reduce LH and FSH output and, in turn, lower testosterone levels [30]. This is possible as the luteinizing hormone (LH) release from pituitary cells is inhibited by the extract from Cola nitida, which may indicate that gonadotropin release is regulated [31]. Fresh Cola nitida contains a glucoside called "kaolin," which hydrolyzes or breaks down dried or mature fruit easily into glucose and caffeine. Cola nitida is rich in xanthine alkaloids, including kolanin, kolatin, theobromine, and caffeine [32]. Kolatin primarily stimulates the heart, whereas caffeine has a stimulating impact on the body overall. It has been shown that theophylline, theobromine, and caffeine found in Cola nitida extract have antioxidant and anti-aging qualities in addition to helping to prevent photodamage and reduce wrinkles making it a potential therapy for inhibition of UV-induced erythema and melanoma [31-33].

### 3.2 Phenolic Alkaloids as an Anticancer

Through individual or combination mechanisms, such as disruption of DNA binding, cell adhesion suppression, cell cycle arrest, interference with signal transduction, and receptor binding, phenolics have the potential to be anticancer agents [34]. These phenolic chemicals include a wide range of herbal polyphenols; research has shown that they have cytotoxic effects on many types of cancers, mostly via inducing apoptosis [35]. Conversely, alkaloids are naturally

occurring bases that include nitrogen and are typically bitter in plants. They exhibit strong pharmacological activity and have intricate molecular architectures [33-35]. Alkaloids do not have a specific name, but they can be divided into two groups: "pseudoalkaloids," which are alkaloids that are not derived from amino acids and may or may not have heterocyclic rings, and "protoalkaloids," which are derived from amino acids and contain a nitrogen atom. "True alkaloids" are those containing heterocyclic rings in their structure; their carbon skeleton is an isoprenoid [35]. Amino acids are the main biosynthetic precursors of true alkaloids and protoalkaloids, and acetate is frequently added to their structures. Although some alkaloids, like nicotine, are liquid at ambient temperature, most alkaloids are colorless and crystalline [36]. It has been discovered that one such alkaloid, 7-hydroxystaurosporine (UCN-01), increases the cytotoxic effects of cis-diamminedichloroplatinum II and causes ovarian cancer cells to undergo apoptosis. Additionally, there is a synergistic effect on apoptosis induction when UCN-01 and 5-fluorouracil are combined [37]. Sugiyama [38] showed that inducing apoptosis and cell cycle arrest during the G1 phase are important factors that determine how sensitive cancer cells are to UCN-01, and that UCN-01 significantly inhibits the G1 phase cell cycle by reducing cyclin expression levels.

### 3.3Catechin

The phytochemical (+)-catechin, which is present in Cola nitida, has demonstrated potential in preventing the spread of cancer. It was shown in experiments to lower γ-catenin protein levels by 58% and to limit invasion of prostate carcinoma cells by 24%. Rich in (+)-catechin, Cola nitida is very popular in Nigeria and West Africa and may have a role in the anticancer effects of this dietary compound. Significant concentrations of this chemical have also been reported in some food varieties like yam, which are staple foods in the area [39].

### 3.4 Flavonoid

A wide range of anticancer actions are exhibited by flavonoids, such as suppression of cancer cell growth and invasiveness, induction of apoptosis and autophagy, cell cycle arrest, and modification of ROS-scavenging enzyme activities [40]. This class of molecules, which is found freely in plants as glycosides, is thought to be the biggest group of naturally occurring phenols. In nature, flavonoids are widely dispersed, with larger concentrations observed in the cell sap of higher plants. They mostly contribute to the pigments in fruits and flowers that are red, yellow,

and blue [41]. Polyhydroxy phenols, like flavonoids, may help lower the risk of breast and colon cancer, according to preliminary research [40,42]. Among the many biological characteristics of flavonoids are their anticancer capabilities. Quercetin, for instance, is a well-studied flavonoid that inhibits cell development to produce cytotoxic effects, which helps reduce tumor growth [41]. Additionally, they control reactive oxygen species (ROS) levels, stifle angiogenesis, trigger apoptosis, block pro-inflammatory pathways and carcinogens, and prevent tumor invasion and growth. The pharmacological efficacy of these substances is hindered by their low solubility, a problem that nanoparticle-based delivery systems seek to solve [42]. In addition, flavonoids have pro- and antioxidant properties, alter apoptotic pathways, modify epigenetic regulation, and protect DNA. Their potential in cancer therapy is highlighted by their ability to increase genomic integrity, control apoptotic caspases, and restore the expression of tumor suppressor genes. One explanation for flavonoids' ability to scavenge oxygen-reactive species is the high concentration of phenolic hydroxyl groups in their chemical structure. Because of the intensive electron exchange made possible by this abundance, substitution reactions with free radicals are made possible, which results in the synthesis of more stable molecules [42,43]. Therefore, the bigger the amount of hydroxyl groups present in a flavonoid, the stronger its oxidant and pro-oxidant properties. When ovarian cancer cells were treated with flavonoids such as luteolin, myricetin, and apigenin, the levels of intracellular ROS increased in a dose-dependent manner in comparison to the control cells that were left untreated. As a result, the cell cycle was stopped, the intrinsic apoptotic pathway was activated, and invasion was inhibited. In a similar vein, it has been discovered that the flavonoid quercetin causes cancer cells to die by raising ROS levels [43].

**3.5Tannins**

Tannins otherwise called tannic acid are polyphenolic macromolecules that attach to and precipitate the proteins in the hides. True tannins and pseudo-tannins are the two main varieties of them, and they are both known to be easily soluble in water or alcohol [44]. True tannins are complex phenolic compounds that can precipitate with gelatin in a 1% aqueous solution and have the typical characteristics of tannins. Simpler phenolics known as pseudo-tannins, like gallic and ellagic acids, resemble tannins in certain ways but are not precipitated by gelatin, in contrast to real tannins [45]. Tannic acid has been connected to the anticarcinogenic qualities of tannins. Tannic acid is derived from Cola nitida and other plant sources. It is a major gallotannin that falls

within the category of hydrolyzable tannins. Numerous pharmacological and biological uses of tannic acid in medicine have been widely recognized [44,45]. Potential anticancer actions against a variety of solid malignancies, such as pancreatic, liver, breast, lung, colorectal, and ovarian cancers, have been identified as one of these effects. Numerous oncological signaling pathways, such as JAK/STAT, RAS/RAF/mTOR, TGF-β1/TGF-β1R axis, VEGF/VEGFR, and CXCL12/CXCR4 axes, are significantly influenced by tannic acid [45,46]. Tannic acid has been shown in the literature to have synergistic anticancer effects and improved chemo-sensitivity in several refractory instances when taken with other traditional chemotherapy medications [46].

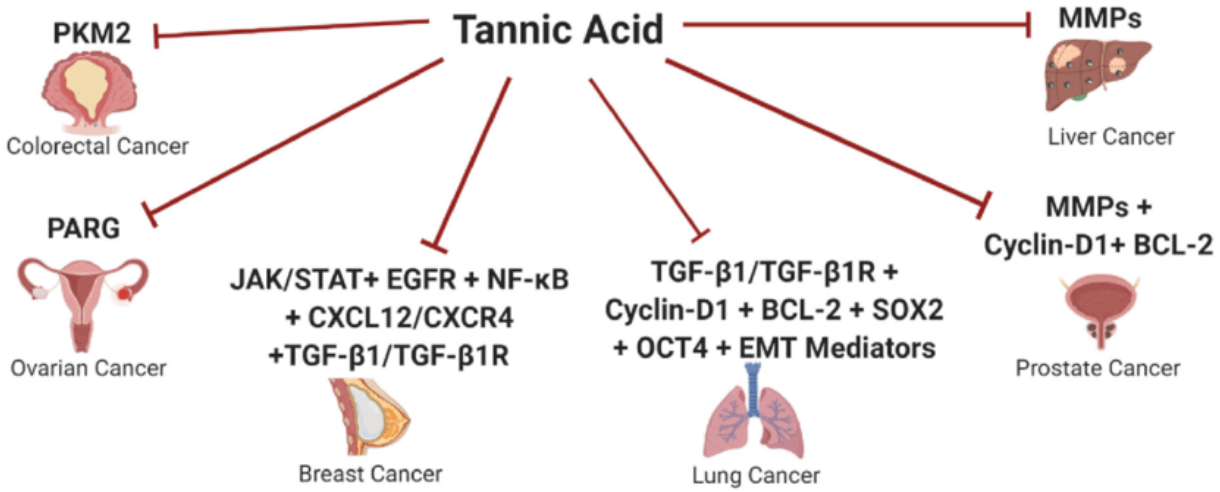


*Figure 3 showing the Molecular Mechanism of Tannin [46].*

Tannic acid (TA) is a suppressor of many proteins involved in different oncological signaling cascades. It prevents TGF-β target gene transcription by blocking SMAD-dependent gene transcription in response to TGF-β. Additionally, TA blocks the VEGF/VEGFR pathway, which is a key route in cancer angiogenesis. Furthermore, TA impedes the development and proliferation of cells by suppressing the expression of the SOX2 gene and blocking the EGF/EGFR signaling pathway. By improving p53's phosphorylation, tannic acid stimulates the expression of target genes including p21 and BAX, hence inducing the production of tumor suppressor proteins. Furthermore, TA can directly promote the expression of the p21 and BAX genes. Moreover, TA increases p27 and p18 gene expression [46].

Tannic acid (TA) exhibits anticancer properties against non-small-cell lung carcinoma (NSCLC) through direct binding to transforming growth factor-β1 (TGF-β1). This results in the regulation of TGF-β1 and its receptor (TGF-β1R), which in turn blocks signaling cascades downstream. Epithelial-to-mesenchymal transition (EMT) mediators and several signaling pathways, including p38, ERK1/2, JNK1/2, Smad2/3, and Akt, are all included in this suppression. TA also affects cell cycle regulatory proteins, reducing cancer stemness markers such as SOX2, OCT4, NANOG, and CD133 and causing cell cycle arrest at the G0/G1 phase [47]. These results demonstrate TA's potential as an anticancer drug against non-small cell lung cancer; nevertheless, additional in vivo investigations are required for confirmation. In prostate cancer (PCa), tannic acid (TA) exhibits strong anti-tumorigenic actions by preventing cellular proliferation, invasion, and migration. By activating IRE1 and PERK, it causes endoplasmic reticulum stress, which in turn causes apoptosis by suppressing pro-survival proteins and changing indicators linked to apoptosis [45, 47]. In addition, TA inhibits the expression of cyclin D1, stops the cell cycle at the G1/S phase, and lowers the amounts of MMP2 and MMP9, suggesting that it may have anti-metastatic properties. Moreover, TA causes disruptions to lipid metabolism, cellular membranes, and the formation of ROS in PCa cells. These results highlight the potential of TA as a PCa treatment strategy [47]. Tannic acid (TA) also exhibits anticancer activity against multiple molecular subtypes of breast cancer (BC) by blocking fatty acid synthase and triggering apoptosis via caspase activation. It causes intrinsic apoptosis and cell cycle arrest by adversely modifying the JAK/STAT and EGFR pathways. Moreover, TA inhibits NF-κB activation and TGF-β-induced EMT, which reduces the activity of cancer stem cells. As an antagonist of CXCL12/CXCR4, it operates to preferentially target BC cells, sparing normal epithelial cells, and impede migration [45-47]. Furthermore, TA reduces the cardiotoxicity caused by doxorubicin and works in concert with paclitaxel, highlighting its potential as a pan-tumor suppressor in the treatment of BC [48]. In liver cancer, tannic acid (TA) demonstrates dual effects as an anti-fibrotic and anticancer drug. Together with cisplatin, it triggers apoptotic pathways in HepG2 cells that result in DNA fragmentation and cell death by mitochondrial-mediated apoptosis. Through its effects on the TIMP/MMP balance, inhibition of hepatic stellate cell activation, and reduction of serum levels of ALT and AST, TA also has hepatoprotective and anti-fibrotic properties. These results point to TA's potential use in the treatment of liver cancer and steatosis [49].

## 4.0 Cola nitida: A Potential Cancer Multimodal Therapy

In contemporary medicine, combining various medications to treat illnesses has shown to be quite beneficial. With this method, disease-causing entities like cancer cells or dangerous viruses are specifically targeted while the body's defense and repair mechanisms are strengthened [50]. This multimodal therapy strategy is frequently used, especially in Western countries, to treat a wide range of complicated diseases, including cancer, inflammatory and metabolic disorders, and infectious diseases like AIDS. Apoptosis, or programmed cell death, is one of the key processes in the emergence of cancer and other illnesses [51]. Through the removal of undesirable or dangerous cells, this natural process is essential for preserving health. On the other hand, illnesses, including cancer, can spread when apoptotic regulation is compromised. Studies have revealed that this disruption plays a crucial role in developing several illnesses in humans [52].

Chemotherapy is a common cancer treatment strategy that primarily uses the apoptotic pathway to kill cancer cells. Nevertheless, despite its effectiveness, there are still many obstacles to overcome, including the development of drug resistance and the harmful side effects brought on by the toxicity of chemotherapeutic medications to healthy cells [53]. Remarkably, almost 60% of anti-cancer medications come from natural sources such as microbes or plants, highlighting the significant potential of nature to provide better treatments. Therefore, research and development activities must continue to create new anti-cancer drugs that target tumor cells with both effectiveness and selectivity [52,53]. Many anticancer drugs can stop malignant cells from growing or cause them to undergo apoptosis. Either direct manipulation of cell-cycle regulating molecules or indirect disruption of many cell signaling pathways are used to accomplish this goal. One of the main factors causing cancer to originate and spread is defective apoptosis. In particular, the Cola nitida extract has demonstrated a great deal of potential. Research has indicated that the extract may be useful as a therapeutic agent for the treatment of cancer, since treated MCF7 cells show a decrease in the cell cycle's development phases and an increase in the populations of apoptotic cells [53]. Furthermore, studies on the chemopreventive properties of C. nitida extract against rats that were given experimentally produced liver cancer indicate that it can reduce cancer development markers in a dose-dependent manner. Studies on animals show a relationship between the degree of cancer severity and certain enzyme activity, suggesting a direct relationship between the two. These results provide credence to the idea that Cola nitida extract could be useful in cancer prevention plans [53,54].

## 5.0 WHO Standard

The World Health Organization (WHO) has worked with African nations over the past 20 years to support the development of traditional medicine safely and efficiently. Both financial and technical support have been given to provide this aid. Consequently, the World Health Organization has supported clinical trials that have resulted in 14 countries approving the marketing of 89 traditional medicine items that satisfy both national and international registration requirements. Notably, national essential medicine lists now contain 43 of these items [55].

These goods are now essential resources for the treatment of a wide range of illnesses in patients, from HIV-related opportunistic infections and malaria to diabetes, sickle cell disease, and hypertension. Nearly every nation in the WHO African region has implemented national traditional medicine policies with support from the WHO. To further advance the integration of traditional medicine into healthcare systems, the World Health Organization (WHO) published standards for evaluating herbal medicine in 1991 [56]. These standards stipulate that herbal medicines must go through clearance procedures that include stability and safety assessment, quality control (for raw herbal complexes, plant preparation, and final products), and the production of required documents for assessing medicine efficacy. As efforts to find cancer treatments advance, it is critical to be vigilant about false information claiming the efficacy of certain treatments, especially on social media. Many plants and chemicals are being promoted without fulfilling the minimal standards or offering proof of their effectiveness, safety, or quality. WHO enthusiastically welcomes the chance to work with nations and researchers to develop novel treatments, and promotes these kinds of collaborations to create safe and efficient treatments for patients in Africa and beyond.

## 6.0 Conclusion

This study highlights the great potential that exists for natural compounds like Cola nitida to be used in the creation of new, more effective, and less harmful cancer treatments. The use of natural substances in cancer therapy is a promising area of research as more is learned about the intricacies of cancer and the workings of prospective remedies. Extending the range of anti-cancer treatments using natural materials not only presents new therapeutic opportunities but also promises less harmful treatment modalities. Examining organic substances such as Cola nitida

extract is an exciting field of study that could have a significant influence on how cancer is treated by introducing novel treatments that could improve survival rates and quality of life for cancer patients globally.

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