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Phytochemistry and pharmacology of *Imperata cylindrica*: A comprehensive review

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Abstract

Background: *Imperata cylindrica* is a medicinal spice used in traditional medicine to cure several ailments including cancer, wounds, hypertension, and inflammation. The current study aimed to compile phytochemicals and pharmacological data on *Imperata cylindrica*.

Methods: A bibliographic study was carried out by analyzing conventional textbooks, authentic published studies, and consulting wide-reaching accepted scientific databases. In this review, an attempt is being made to establish an up-to-date chemical profile of *I. cylindrica* and the classification of its compounds in the main classes of plant secondary metabolites. Moreover, our study highlights the traditional usage of *I. cylindrica* and the reported investigations regarding the pharmacological properties of this plant.

Results: The 43 phytochemicals isolated by various investigators mainly from the roots of *I. cylindrica* could be classified as bioactive phenolic compounds (coumarins, flavonoids, phenols, lignan glycosides, nor-lignans, phenolic acids, and aurone), few of them also belong to the group of terpenoids (sesquiterpenoids and triterpenoids), steroids and phytosterols. Based on the examined published data, the roots, and leaves of *I. cylindrica* are outstanding cytotoxic agents against several sensitive and resistant primary cancers through apoptosis induce, G1 cell cycle arrest (roots), and G2/M cell cycle arrest (leaves). Moreover, the root extract prevents metastasis invasion through inhibition of the PI3K/AKT/Snail pathway and the epithelial to mesenchymal transition (EMT) process *via* modulation of certain key genes. *I. cylindrica* tackles the growth of sensitive and multidrug-resistant (MDR) pathogenic microorganisms from various species and potentiates the antimicrobial activities of certain families of antibiotics towards MDR bacterial strains. The plant also has significant antihypertensive, anti-hyperglycemic, anti-parasitic, antioxidant activity, and several other pharmacological properties. Various studies characterized the *Imperata cylindrica* root extract as non-toxic to humans by oral route.

Conclusion: From the outcome of this review, *I. cylindrica* is a potent candidate for drug formulation against primary and metastatic cancers, some drug-resistant microbial infections, and hypertension.

Keywords: *Imperata cylindrica;* phytochemicals; Pharmacology; Cancer; Microbial infections; Hypertension.

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Background

Human life is under constant threat from diseases of all kinds. According to the World Health Organization (WHO), non-communicable diseases (NCDs), mainly cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases are the leading cause of death worldwide. They represent 7 of the 10 main causes of death equivalent to 74% of all deaths globally. This includes more than 15 million people who die prematurely every year from a major NCD between the ages of 30 and 69 years. Communicable diseases, including HIV/AIDS, tuberculosis, malaria, viral hepatitis, sexually transmitted infections, and neglected tropical diseases, are among the leading causes of death and disability in low-income countries and marginalized populations [1]. The early diagnosis and the constant discovery of drugs are efficient strategies to fight against diseases and preserve human life. Drug discovery sources are very diverse: identification of active metabolites from traditional remedies or by the serendipitous discovery (penicillin), chemical libraries of synthetic small molecules, screening of natural products or plant extracts and their derived compounds [2]. Natural products constitute a leading source of several new drugs and active ingredients in medicines [3-20]. Over the past 20 years, more than one-third of the therapeutic agents approved by the US FDA were derived or inspired from natural products and more than 50% of the developed small-molecule drugs from 1981 to 2014 originated from natural products, semi-synthetic natural products, and natural products derived [21]. In their living environment, plant species are regularly exposed to stressful conditions due to abiotic factors including salinity, nutrient deficiency, excessive radiation (UV-light, solar radiation), drought, water logging and flooding, extreme cold or hot temperature, soil pH and anthropogenic pollutants or biotic stresses include herbivory by vertebrate and invertebrate grazers, as well as diseases caused by microbes such as fungi, bacteria, and viruses, and competition among plants [22]. These stress factors induce morphological, physiological, biochemical, and molecular changes in plants, affecting their growth [23]; to survive under such difficult and stressful conditions, they undergo some important modifications like changes in signaling components gene transcription, non-coding RNAs, proteins, and the upregulation of genes and pathways involved in the synthesis of some important classes of secondary metabolites, most often used as drugs due to their proven pharmacological activities [24]. In the current study, we are focused on a dietary plant used in cuisine, as a source of molecules endowed with tremendous pharmacological properties against several human diseases: *Imperata cylindrica,* commonly known as Cogon grass, a perennial rhizomatous grass native to Southeast Asia and widespread invader in many subtropical and tropical regions [25]. To date, numerous studies have revealed the usefulness of this grass to fight against several diseases including primary cancers, microbial infections, hypertension, and many others. Phytochemical investigations of this plant have led to the isolation of various pharmacologically active compounds. The focus of this paper is to provide an updated review of the phytochemical studies that have addressed the isolation and identification of chemical compounds from *Imperata cylindrica,* and those that have revealed pharmacological activities.

Methods

This literature review was conducted using research articles and books available on various scientific databases such as Google Scholar, Embase-Elsevier, PubMed, Science Direct, Scopus, Web of Science, Global Invasive Species Database and World Checklist of Selected Plant Families. We have reviewed authentic research literature published between the years 1984-2022.

Results and Discussion

Ecological distribution and botanical description of I. cylindrica

Imperata cylindrica is a perennial rhizomatous grass commonly known as “cogon grass’’ or “speargrass’’ or “Japanese blood grass’’. It is a native plant to Southeast Asia and a widespread invader in many subtropical and tropical regions [25] which usually grows in warm or tropical areas and is widely distributed in Africa, Asia, Australia, Europe, North America, and South America as shown in Figure 1 [26]. Cogon grass is a stemless erect perennial growing in loose to compact tufts with slender flat linear-lanceolate leaves arising from the rhizomes. The scabrous leaves are 4 to 10 mm wide with prominent white midribs that are slightly off-center. The leaves maybe 15 to 150 cm long, depending on habitat, with narrow sharp points [27], and most of its biomass is constituted by its roots/rhizomes found below ground [28]. Figure 2 displays the pictures of Congo grass.

Taxonomy of I. cylindrica

Imperata cylindrica was first described by Linnaeus in 1759 under the basionym *Lagurus cylindricus* [29] and later renamed by the French entomologist and Botanist Palisot de Beauvois to the currently accepted name of *Imperata cylindrica*. However, according to the Global Invasive Species Database [30], this plant has several other synonym names. Table 1 shows the taxonomy of Cogon grass as described by the World Checklist of Selected Plant Families [31].

Phytochemical profile of I. cylindrica

Most often, the motivation for the isolation of plants’ compounds is the outstanding pharmacological activity of its crude extract. Most plant bioactive chemicals could be distributed in three main classes based on their biosynthesis pathways: terpenes and terpenoids, phenolic compounds, and alkaloids**.** Terpenes synthesis happens *via* mevalonic pathway from the precursor of acetylcoA, while phenolic compounds are aromatic substances formed *via* the shikimic acid pathway or the mevalonic acid pathway, and alkaloids are synthesized primarily from aliphatic amino acid derived from the tricarboxylic acid cycle or aromatic acids derived from the shikimic acid pathway [32]. From the investigations of many authors, a great number of compounds have already been isolated from *Imperata cylindrica*, mainly from the roots and the leaves. This part of our investigations focused on the identification and classification of the reported phytochemicals of *I. cylindrica* in the aforementioned classes of secondary metabolites.

Phenolic compounds from I. cylindrica

Phenolic compounds are a group of small molecules characterized by their structures having at least one phenol unit. Based on their chemical structures, phenolic compounds can be divided into different subgroups, such as phenolic acids, flavonoids, tannins, coumarins, lignans, quinones, stilbenes,

and curcuminoids. Figure 3 depicts the structures of phenolic compounds isolated from *I. cylindrica* by various investigators.

Flavonoids

Flavonoids are composed of two aromatic rings linked by a unit of three carbon atoms (C6-C3-C6). This carbon skeleton is the explanation for the chemical diversity of this family of compounds. The basic structures of flavonoids are aglycones but in plants, most of them are glycosides [33]. Four flavonoids compounds have been isolated by Liu et al. [34] from the hydroethanolic root extract (30:70) including 6-hydroxy-5-methoxyflavone (**1**), 5-methoxyflavone (**2**) and 5,7- dihydroxy-8-methoxyflavone (**3**). Khaerunnisa et al. [35] have isolated and identified 7,3',5'-trime-thoxyflavonol (**4**) from a methanolic root extract of *I. cylindrica.* Wang et al. [36] identified tricin (**5**), a flavone compound from the aerial part ethyl acetate extract of *I. cylindrica.* The recent work of Nago et al. [37] on the chemistry of the methanolic extract *I. cylindrica* root reported the isolation of three flavonones namely cylindricin A (**6**), cylindricin B (**7**) and mearnsetin (**8**). The same work also led to the isolation of a flavonol : 3',4', 5,5',7-pentahydroxyflavanone (**9**).

Coumarins

Coumarins are polycyclic aromatic compounds containing a 1-benzopyran moiety with a ketone group at the C2 carbon atom (1-benzopyran-2-one) **(**Musiliyu et al., 2008). The coumarins by Liu et al. [34] from the hydroethanolic root extract (30:70) of *I. cylindrica* include 4,7-dimethoxy-5-methylcoumarin (**10**), 7-hydroxy-4-methoxy-5- methylcoumarin (**11**), and 7-*O*-*β*-$_D$-glucopyranosyl- 4-methoxy-5-methylcoumarin (**12**).

Phenols

Phenols are a class of chemical compounds consisting of one or more hydroxyl groups (-OH) bonded directly to an aromatic hydrocarbon group [38, 39]. The simplest is phenol, C_6H_5OH. From the hydroethanolic root extract (30:70) of *I. cylindrica,* 4-hydroxybenzaldehyde (**13**) was isolated [34]. Two *diphenylethers* were isolated by Matsunaga et al. Matsunaga et al. (1994a) from the hydro-methanolic (50:50) root extract of *I. cylindrica:* cylindol A (**14**) and B (**15**). Gas chromatography-mass spectrometry analysis of the chloroform extract of *I. cylindrica* indicated the presence of 2-methoxy-4-vinylphenol (**16**) and phenol,2,4-bis (1,1-dimethylethyl) (**17**) [40].

Phenolic acids

Phenolic acids are one of the main classes of phenolic compounds found in plants and occur in the form of esters, glycosides, or amides, but rarely in free form. The structural variation of phenolic acids depends on the number and position of hydroxyl groups on the aromatic ring. Phenolic acids have two distinctive structures: hydroxycinnamic and hydroxybenzoic acid. Phenolic acid compounds isolated and identified by An et al. [41] from the root methanol extract include 7-hydroxy-5-methoxy-2-methyl-chromone (Isoeugenin) (**18**), 4-hydroxy-3-methoxycinnamic acid (ferulic acid) (**19**), 4-hydroxycinnamic acid (p-coumaric acid) (**20**), and 3,4-dihydroxy-cinnamic acid (caffeic acid) (**21**). Moreover, the study of Liu et al. [34] led to the isolation of 4-hydroxy-cinnamic acid (**22**) and 4-hydroxy-3-methoxybenzoic acid (**23**). Wang et al. [42], have also identified *p*-coumaric acid from the aerial part ethyl acetate extract of *I. cylindrica.*

Lignans

Lignans are a large group of naturally occurring phenols that are widely spread within the plant kingdom. These compounds show dimeric structures formed by a β, β′-linkage between two phenyl propane units with different degrees of oxidation in the side chain and a different substitution pattern in the aromatic moieties [43]. The investigation carried out by Lee et al. [44] on the hydro-methanolic (20:80) roots extract of *I. cylindrica* led to the isolation and identification of 6-acetyl-1-[1,3-(4,4′-dihydroxy-3,3′-dimethoxy-*β*-truxinyl)-*β*-$_D$-fructofuranosyl]-α-D-glucopyranoside (impecyloside A) (**24**). The study conducted by Matsunaga et al. [40] on the root hydromethanolic extract (50:50) of Cogon grass has led to the isolation and identification of a nor-lignan called Imperanene (**25**).

Aurones

Aurones [2-benzylidenebenzofuran-3(2H)-ones] are the secondary metabolites natural compounds belonging to the flavonoid family, and structurally are the isomers of flavones, widely present in fruits and flowers where they play a significant role in the pigmentation of the part of the plant in which they occur [45]. Phytochemical studies carried out by Nago et al. [37] on the methanolic extract of *I. cylindrica* root indicated the isolation of a bioactive aurone: cylindraucine (**26**).

Terpenoids from I. cylindrica

Terpenoids, the largest family of natural products with more than 40,000 structures, refer to a large class of oxygen-containing terpene analogues that can be found in all classes of living things. Similar to terpenes, they are all derived from five-carbon isoprene units assembled and modified in different ways [46-49]. The investigations of Matsunaga et al. Matsunaga et al. (1994b) investigated hydro-methanolic (50:50) root extract of *I. cylindrica* led to the isolation and identification of a sesquiterpenoids: [1-(3-hydroxy-3-methyl-7-propan-2-yl-1,2-dihydroinden-5-yl)ethenone)] (cylindrene)(**27**) as a colourless oil. The *n*-hexane root extract of *I. cylindrica* afforded several triterpenoids including 14-epiarbor-7-en-3β-ol (**28**), 14-epiarbor-7-en-3β-yl formate (**29**),14-epiarbor-7-en-3-one (**30**), cylindrin (**31**), arundoin (**32**), *α*-amyrenone (**33**), β-amyrenone (**34**), fernenone (**35**), arborinone (**36**), isoarborinol (**37**) and fernenol (**38**) [50]. Nago et al. [37] recently isolated a C-15 isoprenoid analogue from the methanolic extract of *I. cylindrica* root : cylindracid A (**39**). Terpenoids isolated from *I. cylindrica* are represented in Figure 4.

Steroids and phytosterols from I. cylindrica

Steroids, derived from the terpenoid building block isopentenyl-pyrophosphate, are a subclass of terpenoids that contain a characteristic arrangement of four cycloalkane rings joined to each other [48]. Wang et al. [42] isolated and identified two steroids from the aerial part ethyl acetate extract of *I. cylindrica:* 11,16-dihydroxy pregn-4-ene-3,20-dione (**40**) and 2-methoxyextrone (**41**). Gas chromatography-mass spectrometry analysis of the chloroform extract of *I. cylindrica* indicated the presence of stigmasterol (**42**) and campesterol (**43**) [51]. Steroids and phytosterols isolated from *I. cylindrica* are represented in Figure 4. Figure 5 depicts the up-to-date statistics on isolated phytochemicals of I. *cylindrica.* Phenolic compounds and terpenoids are the groups of chemicals mostly isolated by researchers from *I. cylindrica*. More than sixty percent (60.46%, 26/43) of the isolated chemicals belong to

phenolics, followed by terpenoids (30.23%, and 13/43, respectively).

Medicinal utilization of Cogon grass in Traditional Medicine

According to the World Health Organization [52], 65 to 80% of the population of developing countries use plants as remedies. Even though *I. cyindrica* is a serious weed not only in crops but also in natural areas, causing serious economic and environmental damage, this grass as a medicinal herb has an important role in traditional medicine. The parts of Cogon grass mostly used by people are the roots followed by the leaves (Table 2). Several investigations carried out by various authors globally have shown the pharmacological efficiency of plant extracts and their derived compounds against various diseases [14, 16, 19, 53-83]. In the present review, the synopsis of the fascinating anticancer, antimicrobial, anti-hypertensive, anti-hyperglycemic activity, and other properties of *I. cylindrica*.

Imperata cylindrica against cancer

Cytotoxic activity against drug-sensitive, drug-resistant, and metastatic cell lines

Cytotoxicity refers to the property of a chemical or biological agent to be toxic against cells, possibly to the point of destroying them [84]. Based on a review discussing the exploration of cancer therapeutics with natural products from medicinal plants, the latter can serve as sources of lead compounds for the development of new anticancer drugs or scaffolds necessary for their synthesis may be found in plants [85]. Several studies on various parts of Cogon grass have revealed its capacity to be used in the fight against several types of primary cancers. The *in vitro* anticancer studies carried on the roots methanol extract of *I. cylindrica* have revealed its outstanding cytotoxic effects against the CCRF-CEM (IC_{50}: 7.99 µg/mL) human acute lymphocytic leukemia [86, 87], and their multidrug resistant (MDR) subline CEM/ADR5000 (7.18 µg/mL) [86]; the HL60 (IC_{50}: 11.66 µg/mL) and HL60AR (IC_{50}: 26.64 µg/mL) human acute promyelocytic leukemia cell lines; the MDA-MB231 (IC_{50}: 6.02 µg/mL) and MDA-MB231/*BCRP* (IC_{50}: 13.08 µg/mL) human breast adenocarcinoma cell lines [87]; the HCT116 $p53^{+/+}$ (IC_{50}: 3.28 µg/mL) and HCT116 $p53^{-/-}$ (IC_{50}: 4.32 µg/mL) human colon carcinoma cell lines ([86, 87]; the U87MG (IC_{50}: 13.10 µg/mL) and U87MG.*ΔEGFR* (IC_{50}: 14.79 µg/mL) human glioblastoma cell lines, the HepG2 (IC_{50}: 33.43 µg/mL) human hepatocarcinoma cell line [86, 87] and the Mia Paca2 (IC_{50}: 12.11 µg/mL) human pancreatic cancer cell line [86]. The *in vitro* studies carried out on the leaves of Cogon grass showed its ability to impair the viability of several cancer cell lines: the methanol leaf extract of *I. cylindrica* kills human oral squamous carcinoma cell line (SCC-9) with av IC_{50} value of 139 µg/mL after 24 h of treatment [88]; three compounds derived from the ethyl acetate leaf extract of *I. cylindrica* displayed a cytotoxic effect (after 72 h of treatment) against the human breast cancer cell line BT-549 (IC_{50} values of 102, 97 and 68 µM respectively for 2-methoxyextrone, 11,16 dihydroxy pregn-4-ene-3,20-dione and tricin) and the human colorectal adenocarcinoma cell line HT-29 (IC_{50} values of 147, 137 and 114 µM respectively for 2-methoxyextrone, 11,16 dihydroxy pregn-4-ene-3,20-dione and tricin) [42]. Moreover, from the *in vitro* investigations of Kwok et al. [89], the crude ethyl-acetate aerial part (leaf) of *I. cylindrica* displayed significant anti-cancer activity against the HT-29 cell line (IC_{50} :14.5 µg/mL). The whole plant of *I. cylindrica* (methanol extract) showed a weak anti-proliferative effect against the human breast cancer adenocarcinoma cell line MCF-7 with an IC_{50} value of 83.10 µg/mL after 24h of treatment [90]. Recent works of Nayim et al. [91, 92] reported the considerable antiproliferative activity of the MeOH extract of *I. cylindrica* root toward the human cervical cancer cell lines SiHa ($IC_{50:}$ 64.89 µg/mL), CaSki (IC_{50} : 50.71 µg/mL), and Hela (IC_{50} : 68 µg/mL). In addition, the authors highlighted the significant and dose-dependent antitumor activity of the crude methanolic extract of *I. cylindrica* at 100, 200, and 400 mg/kg body weight against a xerograph model of cervical cancer (CaSki) [91].

Mechanisms and therapeutic implications of cell death induction and metastasis inhibition by I. cylindrica

Mechanisms of cell death induction and metastasis inhibition

The hallmarks of cancer comprise biological capabilities acquired during the multistep development of human tumors [43]. They include sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [93]. The potential activity of a test substance against cancer, such as a plant extract or secondary metabolite, is not only associated with the cytotoxic or antiproliferative effect but is also related to the ability to inhibit mechanisms concerning the above-mentioned hallmarks. Most investigations regarding the anticancer activity of *I. cylindrica* have highlighted apoptosis linked to cell cycle arrest. From the *in vitro* study conducted by Kuete et al. [87], the root methanol extract of *I. cylindrica* induced G_1 cell cycle arrest and apoptosis via the alteration of mitochondrial membrane potential in CCRF-CEM human acute lymphocytic cell line at the following concentrations: 1/2 × IC_{50} (3.99 µg/mL), IC_{50} (7.99 µg/mL) and 2 × IC_{50} value (15.98 µg/mL). The leaves ethyl acetate extract of *I. cylindrica* displayed G2/M cell cycle arrest and apoptosis *via* the accumulation of reactive oxygen species (ROS) in HT-29 human colorectal cancer cell line when treated at IC_{50} value (7.99 µg/mL) [89]. Moreover, the *in vitro* investigations conducted by Keshava et al. [88] have revealed the apoptotic effects of leaf methanol extract of *I. cylindrica* in the SCC-9 human oral squamous carcinoma cell line through DNA fragmentation when treated at 320 and 640 µg/mL, and the methanol extract of *I. cylindrica* was found to promote apoptosis in MCF-7 [89]. Recent work of Nayim et al. [92] also reported the significant apoptotic effects and G0/G1 cell cycle arrest of the methanol extract of *I. cylindrica* root toward the human cancer cervical cell line CaSki at concentrations equal to its IC_{50} and 2 × IC_{50} value on this cell line.

Metastasis referred to the spread of cancer cells from the primary tumor to surrounding tissues and to distant organs and is the primary cause of cancer morbidity and mortality. It is estimated that metastasis is responsible for about 90% of cancer deaths (Chaffer et al., 2011). Therefore, molecules or plant extracts that could tackle metastasis are of great interest in the ongoing battle against cancers. Recent investigations conducted by Nayim et al. [91] revealed the strong *in vitro* anti-metastatic effect of the methanol extract of *I. cylindrica* root against the human cervical cancer cell lines CasKi at concentrations ranging from 30 to 60 µg/mL. In their findings, the crude extract significantly impaired the migration and invasion of CaSki cells using the following mechanisms of action: Blockage of the epithelial to mesenchymal transition (EMT) through downregulation of clinically high-risk metastasis-promoting gene CD24, inhibition of phosphatidylinositol 3-kinase (PI3K)/AKT pathway, and *via* the TIMP-4 gene upregulation and inhibition of Matrix metalloproteinases (MMP7, MMP2, MMP7, MT1-MMP). Furthermore, the extract was also inhibiting the epithelial to mesenchymal transition *in vivo* using a

mouse model [91]. Based on the above-described findings, we attempted to elucidate the general mechanism of action of *I. cylindrica* against primary cancers and metastasis (Figure 6).

Anticancer chemotherapeutic implications

One of the most common treatment options for several cancer types is chemotherapy, which uses drugs to kill cancer cells. Chemotherapy may help to treat cancer, prevent it from returning, stop it from spreading, and/or delay its growth. Advances in cancer chemotherapeutics implies the discovery of substances capable of significantly interfering with cancer hallmarks and certain cellular signaling pathways that are frequently deregulated in most cancers. Apoptosis defects may allow epithelial cells to survive in a suspended state, without attachment to extracellular matrix which facilitate metastasis [94]. Successful eradication of cancer cells by nonsurgical means is ultimately approached *via* induction of apoptosis. All the cancer drug designers try either to activate the inactivated apoptotic mechanism or rectify a defective one. Furthermore, all cytotoxic anticancer therapies currently in clinical use, when they work, induce apoptosis of malignant cells [95]. A number of pharmaceutical companies have developed PI3K isoform-specific inhibitors to tackle cancers. As of January 2019, three PI3K inhibitors are approved by the FDA for routine clinical use in humans: the PIK3CD inhibitor idelalisib (July 2014, NDA 206545), the dual PIK3CA and PIK3CD inhibitor copanlisib (September 2017, NDA 209936), and the dual PIK3CD and PIK3CG inhibitor duvelisib (September 2018, NDA 211155) [96-99]. Therefore, extracts and molecules that interfere with the process of metastatic invasion are of great interest since metastasis represents the primary cause of death in cancer patients. Among the reviewed scientific papers on the anticancer properties of *Imperara cylindrica* and its compounds, it appears that *I. cylindrica* and its chemicals force apoptosis and induce cell death in many cancer types. In addition, *I. cylindrica* inhibits the metastasis of cancers *via* the blocking of the phosphatidyl inositol 3-kinase-AKT-Snail pathway. This signaling pathway is an intracellular signal transduction pathway that promotes metabolism, proliferation, cell survival, growth, and angiogenesis in response to extracellular signals. It is important to mention that the PI3K-AKT pathway is one of the cellular signaling pathways mostly dysregulated in cancers and their metastasis. Thus, killing malignant cells through inhibition of the PI3K-AKT signaling pathway and apoptosis induce, makes *I. cylindrica* a potential natural drug to efficiently tackle early-stage cancers and late-stage neoplasms (metastasis).

I. cylindrica against sensitive and multidrug-resistant bacteria

Microbial infection refers to the invasion of a host's tissue by a pathogenic microorganism. The fight against bacterial infections is becoming more difficult because of the rapid emergence of resistant strains of microorganisms occurring worldwide, endangering the efficacy of antibiotics [100]. Moreover, the first antimicrobial resistance surveillance data published by the World Health Organization have shown high levels of resistance to several serious bacterial infections in both high- and low-income countries {(WHO)., 2019 #6637}. Several studies have reported the antimicrobial effects of the roots, leaves, and whole plant extracts of *I. cylindrica* against many sensitive and resistant microorganisms. Investigations of Voukeng et al. [101] have revealed the *in vitro* antibacterial activities of the roots methanol extract of *I. cylindrica* against the following Gram-negative multidrug-resistant (MDR) bacteria with minimal inhibitory concentration (MIC) and minimal bactericidal concentration ranging from 256 to 1024 μg/mL: *Escherichia coli* ATCC 8739, ATCC 10536, AG 100, AG 100A, AG 100A_{TET} , AG012, MC 4100, W3110; *Enterobacter aerogenes* ATCC 13048, CM64, EA27, EA289, EA293, EA3; *Enterobacter cloacae* BM47, BM67, ECCI69; *Klebsiella pneumoniae* ATCC 12296, K2, K24, KP55, KP63; *Providencia stuartii* ATCC 29916, NEA16, PS2636, PS299645 and *Pseudomonas aeruginosa* PA01, PA124. The study of Badawe et al. [102] has shown the *in vitro* anti-staphylococcal activity of the methanol roots extract of *I. cylindrica* towards a panel of resistant *Staphycoccus aureus* ATCC 25923, SA01, SA18, SA23, SA36, SA56, SA68, SA114, SA116, SA126*; Methicillin-resistant Staphylococcus aureus (MRSA)* MRSA3, MRSA4, MRSA6, MRSA9, MRSA11, MRSA12, *and methicillin-susceptible Staphylococcus aureus (MSSA) strains including* MSSA1. The minimal inhibitory concentration values ranged from 512 to 2048 μg/mL as per their report. Moreover, this plant extract was found to potentiate at sub-inhibitory concentrations, the activities of tetracycline, chloramphenicol, ciprofloxacin, and ceftriaxon against some of the above listed Gram-positive MDR bacteria, with modulating effects ranging from 2 to 16. The research conducted by Nago et al. [37] highlighted the considerable antibacterial activity (16-512 μg/mL) of six phytochemicals isolated from the root of *I. cylindrica* against the MDR phenotypes *E. coli* (ATCC 8739, AG 102), *Enterobacter aerogenes* (ATCC 13048, EA27), and *Staphylococcus aureus* (ATCC 25923, MRSA1): cylindraucin, cylindricin A, cylindricin B, cylindracide A, 3',4', 5,5',7-pentahydroxyflavanone and mearnsetin. From the *in vitro* study of Vignesh et al. [103], the leaf aqueous extract and the leaf ethanol extract of *I. cylindrica* inhibited the growth of *E. coli* and *Staphylococcus aureus* with inhibition's zones of 20, 19, 14 and 14 mm respectively. Ismail et al. [104] have demonstrated the *in vitro* antibacterial activity of *I. cylindrica* (1 to 50 mg/mL) against the following sensitive bacterial strains, *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus,* with diameter inhibition zones ranging from 6.33 to 11.65 mm (leaf methanol extract), 6.33 to 9.67 mm (leaf chloroform extract), 6.33 to 9.67 mm (leaves PBS extract), 6.33 to 8.00 mm (root methanol extract) and 6.33 to 8.33 mm (root chloroform extract). The *in vitro* investigations conducted by Sudha et al. [90] on the whole methanol extract of *I. cylindrica* (2 to 10 μg/μL) have shown its ability to inhibit the growth of *Staphylococcus aureus, Bacillus cereus, Pseudomonas aeruginosa* and *Proteus vulgaris* with inhibition zone's ranging from 6.1 to 7.6 mm. The *in vitro* study carried out by Oji et al. (2017) on the aqueous leaf extract of *I. cylindrica* has revealed the antimicrobial effects of this dietary plant against *Escherichia coli* NCTC 1048, *Enterobacter aerogenes*, *Proteus vulgaris*, *Bacillus specie*, *Salmomonella species* with MIC values ranging from 0.0625 to 0.25 mg/mL and MBC values from 0.125 to 0.5 mg/mL (chloroform extract); *E. coli* NCTC 1048, *S. aureus* NCTC 6571*, Proteus vulgaris* and *Enterobacter aerogenes* with MIC values of 0.25 mg/mL and MBC values of 0.125 to 0.5 mg/mL (methanol-chloroform extract). The work carried out on *I. cylindrica* by Fatima et al. [105] demonstrated the antibacterial effects of this specific plant against a panel of bacteria made up of *E. coli* ATCC 25922 and *S. aureus* ATCC 2593*, Listeria monocytogenes* ATCC 13932*, Bacillus spizizenii* ATCC 6633, and *Salmonella thyphi* with inhibition zones of 5 to 7 mm (acetone extract) and 7 to 8 mm (ethanol extract). The investigation done by Zulfiana et al. (2020) has shown the antimicrobial effects of *I. cylindrica* paper coated with anionic nanocellulose crosslinked with cationic ions against the Gram-negative *Escherichia coli* and *Salmonella typhi* as well as Gram-positive of *S. aureus* and *Bacillus subtilis* bacteria. In the experiment conducted

by Lalthanpuii et al. [51], the roots methanol extract of *I. cylindrica* was effective against *P. aeruginosa* (8 mm), *K. pneumoniae* (8 mm), and *Bacillus subtilis* (10 mm).

I. cylindrica against fungal infections

The work carried out on *I. cylindrica* by Fatima et al. [105] has demonstrated its antifungal effects against *Wickerhamomyces anomalus, Mucor spp., Aspergulus flavus*, *Saccharomyces cerevisiae,* with inhibition zones of 7 to 11 mm (acetone extract) and 7 to 12 mm (ethanol extract). Investigations of Dzoyem et al. [106] have shown the antifungal effects of the methanol-dichloromethane extract of *I. cylindrica* against the following fungi, with MIC values ranging between 1.56 to 6.25 mg/mL: *Candida albicans*, *Cryptococcus neoformans, Candida tropicalis*, *Candida krusei, Candida parapsilosis*, *Candida lusitaniae*, *Candida guilliermondii* and *Candida glabrata.* The aqueous roots and shoot extracts of *I. cyindrica* exhibited variable potential in reducing the *in vitro* mycelial growth of *Fusarium solani* [107].

I. cylindrica against hypertension

Systemic arterial hypertension is the most important modifiable risk factor for all-cause morbidity and mortality worldwide and it is associated with an increased risk of cardiovascular diseases. It is generally defined in adults as systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg. Hypertension can result in heart disease, vascular, disease, stroke and /or chronic kidney disease [108]. Investigations conducted by Mak-Mensah et al. [109] showed a significant dose-dependent vasodilative antihypertensive properties of *I. cylindrica* (EC_{50}=0.013) in an animal model, with a mechanism of action like that one of adrenaline. The methanolic root extract of *I. cylindrica* in NaCl (60 and 90 mg/Kg b.w.) displayed an antihypertensive effect by decreasing the heart rate and amplitude stroke heart volume in *Wistar* rats after 14 days of treatment [110]. Moreover, the decoction of *I. cylindrica* was found to prevent hypertension-induced left ventricular hypertrophy through the reduction of reactive oxygen species production *via* the oxidative stress-related cardiac-NADPH oxidase-dependent pathway (Figure 7) in rats after 5 weeks of daily administration of 5.4 mg [111].

I. cylindrica against hyperglycemia

Diabetes mellitus, commonly known as diabetes, is a group of metabolic disorders characterized by high blood sugar levels over a prolonged period [112]. The methanol extract of roots *I. cylindrica* (90 mg/Kg) showed an anti-hyperglycemic activity through the decrease of glucose absorption level in the intestine of rats [113]. In the work of Mu'nisa et al. [114], the administration of 75% ethanol extract of *I. cylindrica* (whole plant, 250 mg/Kg bw) has reduced the blood glucose levels of mice by 22-27% after 14 days of oral treatment. Moreover, the study conducted by Mu'nisa et al. [115] has shown the capacity of the leaf's methanol extract of *I. cylincrica* to reduce 47-49% the glucose blood levels of hyperglycaemia mice Mus *musculus L*, at doses of 150 and 250 mg/Kg bw.

I. cylindrica against oxidative stress

Padma et al. [116] assessed the antioxidant activity of the methanolic root extract of *I. cylindrica* by using various *in vitro* models of antioxidant activity: the extract was found to have a strong reducing power and the activity was comparable to that of ascorbic acid. The hydrogen peroxide scavenging capacity of *I. cylindrica* was reported as an IC_{50} value of 185.6± 1.551 µg/mL as compared to the IC_{50} value of the standard ascorbic acid 128.5 ± 0.683 µg/mL. In another study conducted by Lalthanpuii et al. [117], the methanol extract of *I. cylindrica* roots showed concentration-dependent scavenging activity on DPPH with an inhibitory concentration (IC_{50}) of 2.14 µg/mL, and similar activity was shown for scavenging H_2O_2, with an IC_{50} of 2.221 µg/mL. Gebashe et al. [118] have also revealed the antioxidant effect of leaf and root extracts of *I. cylindrica*.

I. cylindrica against parasites

In the study conducted by Parvathy et al. [119], the root methanolic extract of *I. cylindrica* exhibited significant anti-helminthic activity in a dose-dependent manner, giving the shortest time in paralysis (3.3 min) and death (6 min) at 80 mg/mL concentration. The study by Oyindamola et al. [120] has revealed the anti-trypanosomal activity of *I. cylindrica* leaves against *T. brucei rhodesiense* (STIB 900) with mean IC_{50} values (µg/mL) of 12.56±0.09, 42.49±0.99 and 30.37±4.40 respectively for hexane extract, ethyl acetate extract, and methanol extract. The *in vitro* test conducted by Lalthanpuii et al. (2019) revealed the antiparasitic effects of *I. cylindrica* against the tapeworm *Raillietina echinobothrida* (chloroform and petroleum ether extracts) and the roundworm *Ascaridia galli* (chloroform extract at 20 mg/mL).

Other pharmacological activities of I. cylindrica

In the *in vivo* study by Robianto et al. [121], the roots ethanol extract of *I. cylindrica* showed a significantly shortening of the estrus phase after 20 days of oral treatment at doses of 90 and 115 mg/Kg bw. The herbal extract powder from *I. cylindrica* reduced body fat mass percentage after 12 weeks of daily administration of 2400 mg (containing 1800 mg of active herbal extract and 600 mg of cyclodextrin) in a randomized, double-blind, placebo-controlled, parallel-group clinical trial performed in overweight Korean adults aged 19–60 years with a body mass index of 25.0–29.9 kg/m^2 (Cho et al., 2017). *In vivo* tests conducted by Khaerunnisa et al. [35] have demonstrated that ethanol root extract (15 mg/200g bw) and ethyl acetate fraction of *I. cylindrica* (15 mg/200g bw) had significantly lowered total cholesterol levels in rats with hypercholesterolemia.

Toxicological studies of I. cylindrica

Despite their pharmacological activities, plants and their constituents could also be harmful to human health [122-124]. Furthermore, some chemical or secondary metabolites produced by plants are toxins like substances, that may cause problems to humans or animals [68, 125, 126]. The poisonous part of the plant can be the seed, root, leaf, stalk, fruit, or the whole plant whereby even a relatively small amount either taken or administered can be harmful to the human body [127]. To be used as drugs to tackle diseases, plant extracts, and their chemicals must be explored to determine their therapeutic doses which do not induce toxicities. Thus, it is useful to gather information regarding the toxicology of *I. cylindrica.* From the acute toxicity study of *I. cylindrica* water extract carried by Chunlaratthanaphorn et al. [128] using rat models, the results indicated an LD_{50} of the plant extract above 5000 mg/ Kg body weight and did not produce observable signs of toxicity during the 14 days of checking. Similar results were obtained by Nayim et al. (2020) as from the results of their acute

oral toxicity assay, the methanolic extract of *I. cylindrica* root was found to be non-toxic with an LD_{50} greater than t 5000 mg/kg body weight. Chunlaratthanaphorn et al. [128] also investigated the sub-chronic toxicity of *I. cylindrica*. The water extract at doses of 300, 600, and 1200 mg/kg body weight orally administered to rats daily for 90 days did cause toxicity based on the examination of histopathology examination, biochemical, and hematological parameters. Nayim et al. [129] orally administered the methanolic extract of *I. cylindrica* to rats at 250, 500, and 1000 mg/kg body weight for 30 days and the study revealed found no significant toxicity following histopathology studies and analysis of biochemical and hematological parameters of animals treated with extract compared to control groups. However, for lo for long-term oral administration, safety measures should be taken as they noticed slight degeneration at a dose of 1000 mg/kg body weight. The study of Konan et al. [130] characterized the *Imperata cylindrica* root and leaf extracts as non-toxic to humans by oral route.

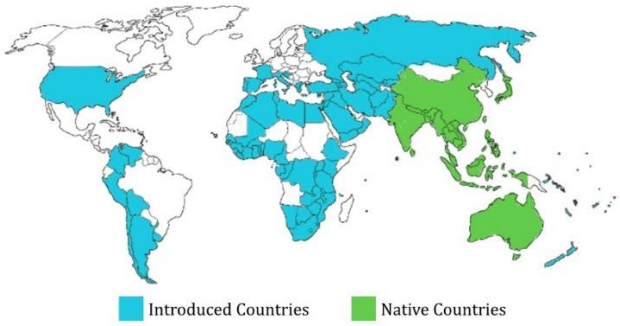

Figure 1. The Ecological distribution of *Imperata cylindrica* throughout the world

Figure 2. Field of *Imperata cylindrica* **(a)** and roots of *Imperata cylindrica* **(b)**

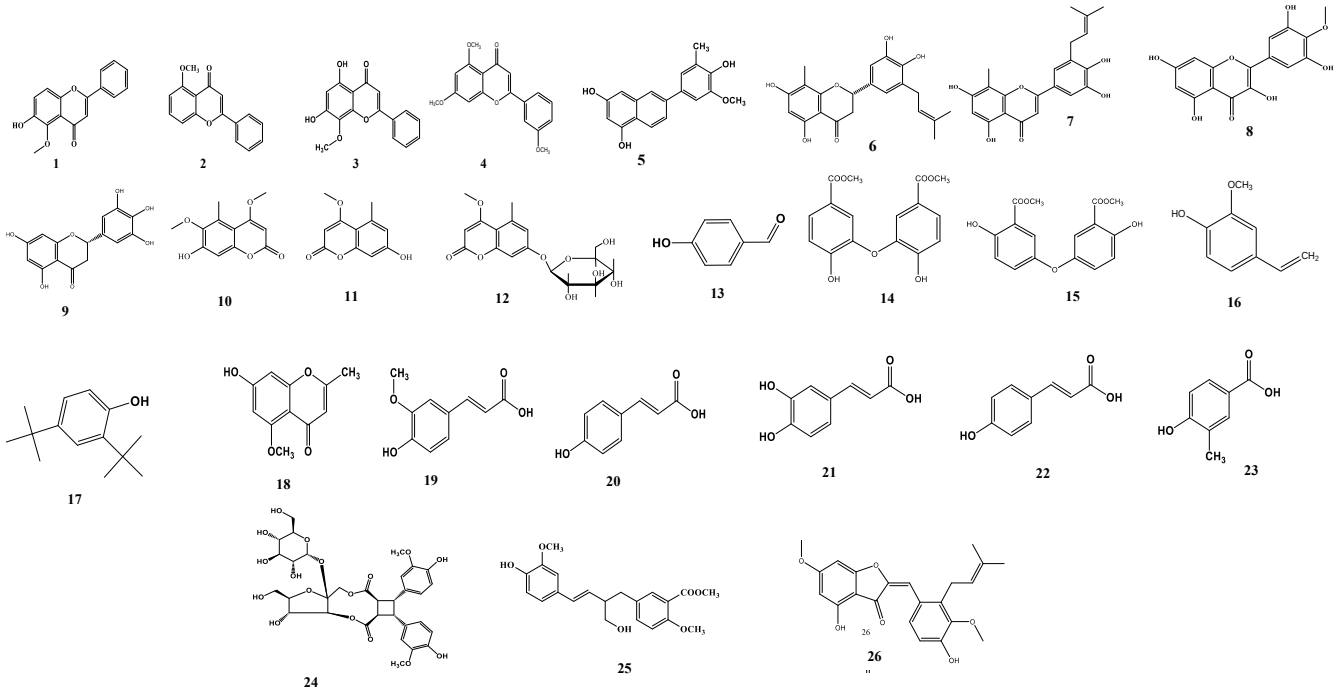

Figure 3. Chemical structures of phenolic compounds isolated from *I. cylindrica*

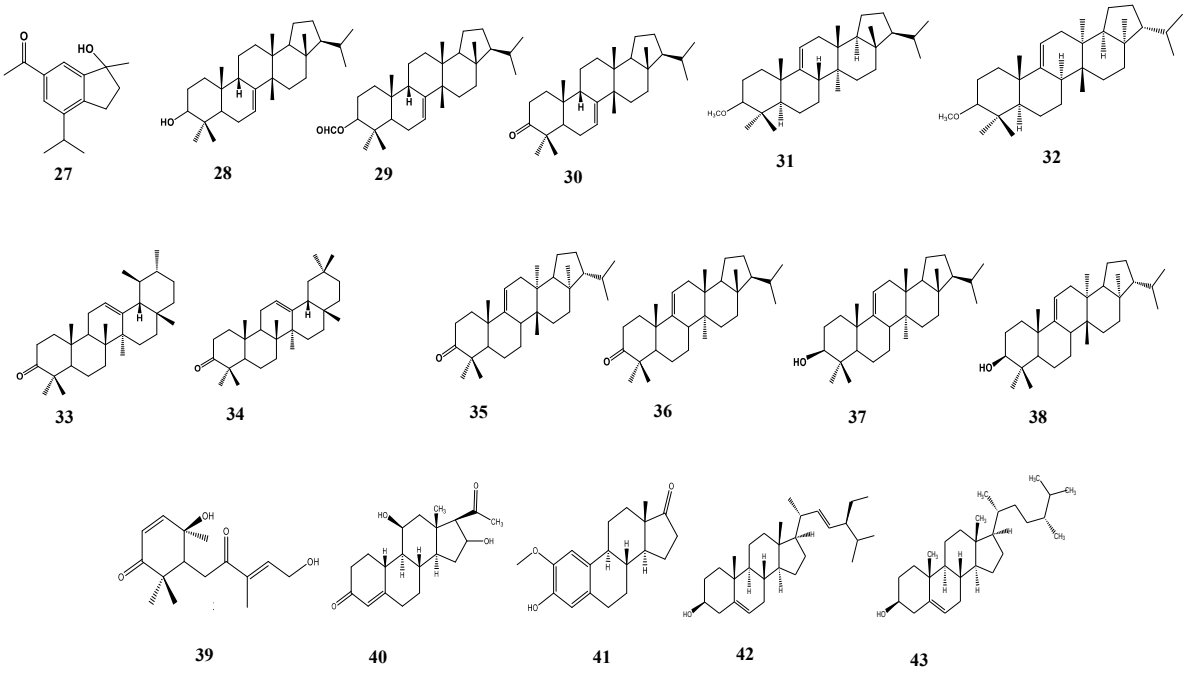

Figure 4. Chemical structures terpenoids, steroids and phytosterols isolated from *I. cylindrica*

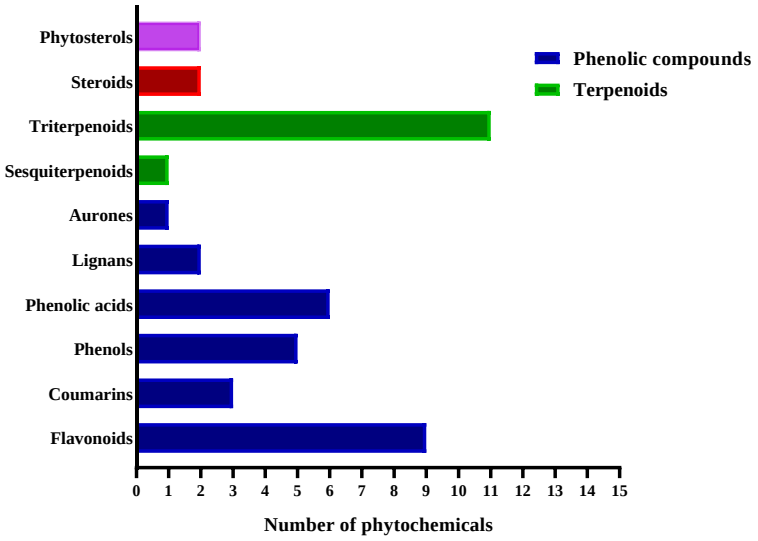

Figure 5. Statistic on the phytochemicals isolated from *I. cylindrica*

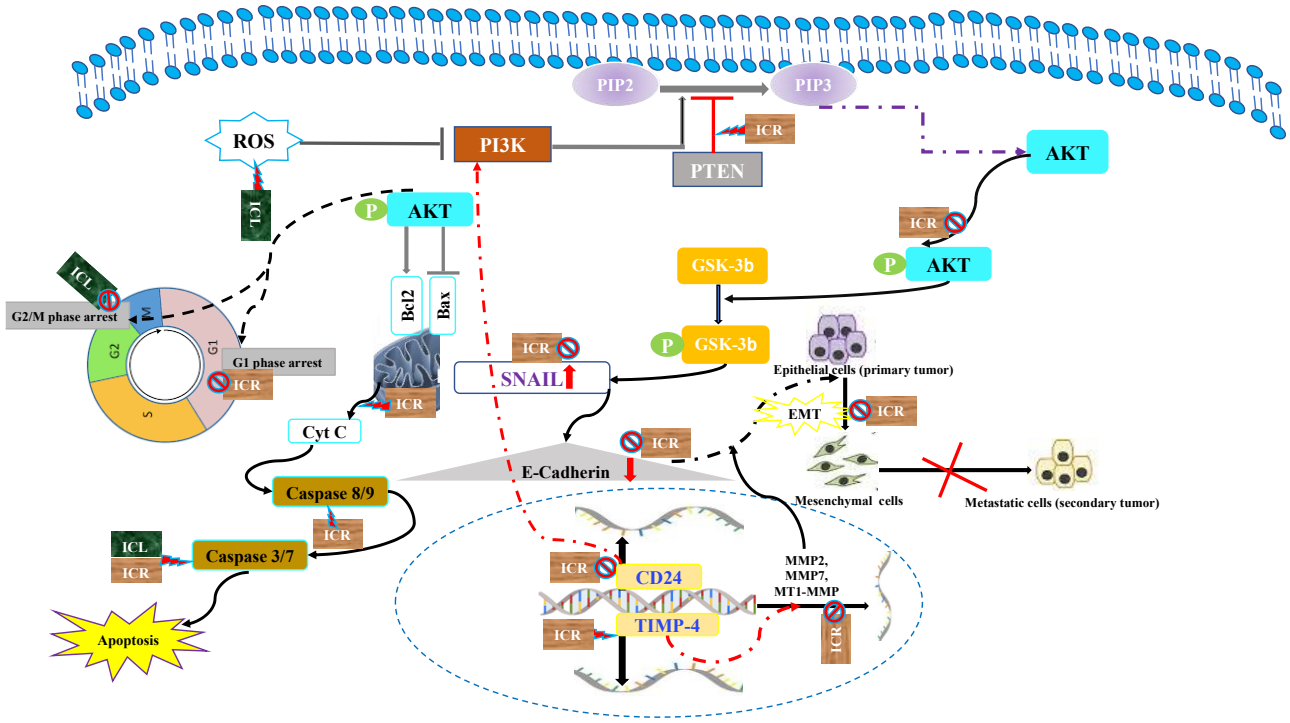

Figure 6. Mechanisms of actions of *I. cylindrica* (root and leaf) toward primary and metastatic cancers.
AKT: Protein kinase B; CD_{24}: Cluster of differentiation 24 (signal transducer); CytC: Cytochrome C; EMT: Epithelial–mesenchymal transition; GSK: Glycogen synthase; ICL: *Imperata cylindrica* leaf extract; ICR: *Imperata cylindrica* root extract; MMP: Matrix metalloproteinases; PI3K: Phosphatidylinositol 3-kinases; PIP_2: phosphatidylinositol-4, 5-bisphosphate; PIP_3: Phosphatidylinositol-3, 4, 5-triphosphate; PTEN: Phosphatase and TENsin homolog; ROS: Reactive oxygen species; TIMP-4: Tissue inhibitors of metalloproteinases. ICR and ICL displayed interesting cytotoxic activity toward various sensitive and resistant cancer cell lines. ICL induces cell cycle arrest at the G2/M phase, and apoptosis through enhancement of reactive oxygen species' production and caspases activation in HT-29 cell line. ICR induces cell cycle arrest at the G0/G1 phase, and apoptosis *via* the alteration loss of MMP in CCRF-CEM cell. Furthermore, ICR prevents the metastatic invasion of cervical cancer through impairment of EMT, inhibition of the PI3K/AKT pathway, transcription's upregulation regulation of the TIM-4 gene, transcription's inhibition of the CD_{24} gene, and some matrix metalloproteinases (MMP2, MMP7, MMP-MT1) genes.

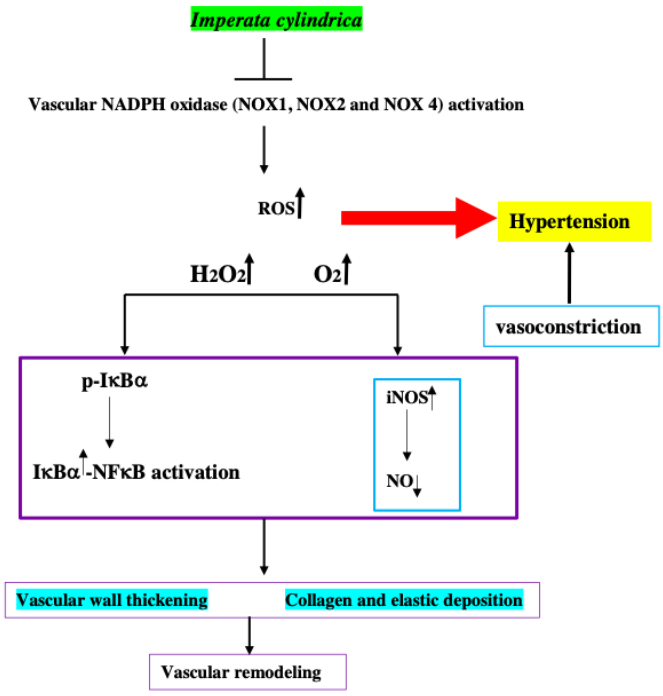

Figure 7. The antihypertensive mechanism of action of *I. cylindrica* [111].
Nox: *Nitrogen oxide*

Table 1. Taxonomy of *Imperata cylindrica*

Domain	Eukaryota
Kingdom	Plantae
Phylum	Spermatophyta
Subphylm	Angiospermae
Class	Monocotyledonae
Order	Cyperales
Family	Poaceae (Graminea)
Genus	*Imperata*
Species	*Imperata cylindrica* (L.) P. Beauv.

Table 2. Medicinal utilization of *Imperata cylindrica* in traditional medicine

Plant part	**Usefulness in traditional medicine**
Roots	Wound [131]
	Sore, ache [131]
	Cancers [10]
	Hypertension [131]
	Fever [131]
	Aphrodisiac ([131]
	Blood urine [132]
	Impotence and jaundice [133]
	Heat burn [134]
	Internal diseases [135]
	Constipation [136]
	Back pain [131]
	Inflammations [137]
Leaves	Wound, sore, aches, scabies [131]
Not explained	Bleeding and toothache [138]
Flowers	Scabies [131]

Conclusion

Secondary metabolites are not necessary for a cell to live but they play an important role in the interaction of the cell (organism) with its environment [131]. The present work highlights the secondary metabolites been isolated by various authors from both the leaves and roots of *I. cylindrica* using methanol, ethanol, ethyl acetate, chloroform, *n*-hexane or a mixture of water, ethanol, water, and methanol. Most of the phytochemicals have been classified in the group of bioactive phenolic compounds: coumarins, flavonoids, phenols, lignin-glycosides, nor-lignans, phenolic acids and aurones. However, some of the isolated chemicals were found to be terpenoids (sesquiterpenoids, triterpenoids), steroids and phytosterols. Plants' secondary metabolites are known for their various biological effects [132], which provide the scientific basis for the use of plants as sources of drugs against several diseases. Phenolic compounds are known for their role in regulating the immune system, their anti-inflammatory effect, chemoprevention, neuroprotection, cardio-protection and in the treatment of diseases such as diabetes, Parkinson's disease, and cancer. In addition to this, they also have interesting antimicrobial. Terpenoids display a wide range of biological activities against cancer, malaria, inflammation, and a variety of infectious diseases. As reported by the works reviewed in this study, *I. cylindrica* is a fascinating cytotoxic toward sensitive and resistant primary cancers, and metastatic cancers. Moreover, *I. cylindrica* has good antimicrobial activity against sensitive and multidrug-resistant pathogenic microorganisms; it also has outstanding anti-hypertensive effects and many other pharmacological properties. This plant must be investigated deeply as a potential candidate for drug formulation, especially its roots which are the most active part and have recently been shown to be safe at lower doses after acute and sub-chronic oral route administration.

Abbreviations

ATCC: American type culture collection; CD_{24}: Cluster of differentiation 24; CytC: Cytochrome C; EMT: Epithelial–mesenchymal transition; GISD: Global Invasive Species Database; GSK: Glycogen synthase; MMP: Matrix metalloproteinases; PI3K : Phosphatidylinositol 3-kinase; PIP_2: phosphatidylinositol-4, 5-bisphosphate; PIP_3: Phosphatidylinositol-3, 4, 5-triphosphate; PTEN: Phosphatase and TENsin homolog; ROS: Reactive oxygen species; TIMP-4: Tissue inhibitors of metalloproteinases.

Author contribution

VK, KS, MS, and ATM., conceptualized the idea. PN performed the literature search and wrote the first draft of the manuscript. BENW drew the compounds' structures. VK, ATM, MS, and BENW. critically reviewed and revised the manuscript. All the authors have read and approved the final version of the manuscript. All authors agree to be accountable for all aspects of work, ensuring integrity and accuracy.

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Conflict of interest

The authors declare no conflict of interest.

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