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CLERODENDRUM INFORTUNATUM: AN UNHEEDED BOON OF NATURE

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ABSTRACT: The excavation for new delegates into the chemotherapeutic family and modernization of existing candidates are evergreen goals of cancer researchers. It is quite interesting to make out that the plant kingdom has gifted us with an array of anti-cancer compounds, reporting over 60% of the drugs today coming out from natural sources such as plants, marine organisms, and micro-organisms. With the evolution of modern analytical tools, the chemical composition of active principle in each of the plant parts is being elucidated, and more plants are being analyzed for their pharmacological application and nominated to the list of medicinal plants. Members of the Verbenaceae family, such as *Clerodendrum infortunatum* crowns in medicinal values tricked with a worthless treasure of phytochemical constituents, many of which remain mysterious. This paper reviews the different aspects of *Clerodendrum infortunatum* concerning its phytochemical constitution, traditional usage, and potential possibilities in the treatment and prevention of cancer. The source materials were browsed from Pubmed and Google by word search for Verbenaceae, Clerodendrum, Cancer, etc. *Clerodendrum infortunatum*, the hill glory bower, is reputed as the prodigious treasure for Indian folk medicine owing to its wide-ranging medicinal applications from the ancient era. This paper reviews the glory of the plant in cancer prevention and chemotherapy due to its importance in the regulation of different "Hallmarks of Cancer". Into the bargain, the articles reviewed here authenticate the anticancer potential of two pentacyclic lupane type triterpenoids, namely betulin and betulinic acid bestowing in the leaves and roots of *C. infortunatum*.

INTRODUCTION: Cancer is a global problem craving for a comprehensive solution. Despite the full-blown skirmishes to get along with the disease, cancer keeps going to take a weird toll on the lives of people all over the world. Cancers of the breast and cervix are two major cancers among women worldwide.

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Among these, at present, cervical cancer incidence has documented a definite decline in many of the developed countries, attributed to the cheering of routine screening programs. But, the calamity remains a major burden in many of the low resource countries.

Even though breast cancer forms a major disease of women in both developed and developing countries, unlike cervical cancer, the mortality rate is getting lowered to a great extent owing to the explosion of many new brands of drugs. Triple-negative breast cancers, comprising about 10-15% of breast cancers characterized by the lack of receptors for targeted therapy, spots an exception to

the above statement showing off the mismatch between drug innovation and disease burden. Henceforth the excavation for new delegates into the chemotherapeutic family and modernization of the existing candidates are evergreen goals of cancer researchers.

It is quite interesting to make out that the plant kingdom has gifted us with an array of anti-cancer compounds, reporting over 60% of the drugs today coming out from natural sources such as plants, marine organisms, and micro-organisms [1, 2]. The anticancer properties of plants have been known for centuries kicking off from the launch of podophyllotoxin. As per the enlistment by National Cancer Institute (NCI) roughly 35,000 plant species possess potential anticancer activities, with almost 3,000 plant species exhibiting reproducible activity [3]. In fact, among the 252 drugs designated as 'basic and essential' by WHO, 11 are exclusively derived from plants. The medicinal action of several plants has been traditionally assessed based on evidence. But with the evolution of modern analytical tools, the chemical composition of the active principle in each of the plant parts is being elucidated and more and more plants are being analyzed for their pharmacological application and nominated to the list of medicinal plants. However, the numbers of plants that reached a druggable level are still very meager.

Members of the Verbenaceae family crowns in medicinal values tricked with a worthless treasure of phytochemical constituents, many of which still remain mysterious [4, 5]. *Clerodendrum infortunatum,* one of the members, was studied by several groups and many of its chemical constituents have been reported to have medicinal values. This paper presents a comprehensive review of the different aspects of *Clerodendrum infortunatum* concerning its phytochemical constitution, traditional usage, and potential possibilities in the treatment and prevention of cancer.

***Clerodendrum infortunatum* L.:**

Taxonomy: The genus *Clerodendrum* represents the group of flowering plants in the Verbenaceae family [6]. The taxonomic description of the plant was reviewed on the basis of data given in India Biodiversity Portal. *Clerodendrum infortunatum* considered as the type species of this genus, is said to be a native of Sri Lanka and the Andaman Islands. The genus is mostly distributed in the tropical and warm temperate regions of the world[7]. *Clerodendrum infortunatum*, a perennial shrub with a displeasing smell, is widely strewn in tropical and subtropical regions of the world, particularly in India. *Clerodendrum calycinum* Turcz., *Ovieda infortunata* (L.) Baill., *Clerodendrum viscosum* Vent., nom. superfl. and *Volkameria infortunata* (L.) Roxb. are the scientific synonyms for the plant. The plant is recognized by diverse vernacular names such as Hill Glory Bower in English, Titabhamt/Bhat in Hindi, and Peruvalam/ Vattaperuvalam in Malayalam.

The plant mostly inhabits waste dwellings and has a global distribution for the most part in moist evergreen forests, on the banks of rivers and nigh villages at an altitude of about 1500 - 5000 feet. The plant has its place in the Verbenaceae family of the Angiosperm clade grouped under order Lamiales of series Bicarpellatae, subclass Gamo-petalae, class Dicotyledons as per Bentham and Hookers classification (1862) [8] whereas it is in the order Verbenales, division Lignosae, subphylum Dicotyledones and phylum Angiospermae by Hutchinson classification (1973) [9]. Further, in 2016, Shipunov has included this family into the sub-order Lamiineae merging with Lamiales.

Morphological Description: The plants exhibit densely hairy, hollow grayish, and lenticellate stem with slender quadrangular branchlets and swollen nodes. The bark is grey and corky. Leaves are simple, opposite, broadly cordate or ovate with an entire margin and 6-9 lateral veins on either side of the midvein. The apex of the leaf is acuminate, showing up a dark-green tomentose dorsal and slightly paler villous ventral side. The petiole is exstipulate, slender, cylindrical, and densely pubescent, measuring about 3-15 cm in length.

The inflorescence is terminal panicles with 6-14 cymes, possessing quadrangular peduncles about 5 cm long with densely pubescent elliptic foliaceous bracts and caduceus bractlets. Flowers are snow-white, lightly fragrant, and tubular. The flowers are bisexual, zygomorphic, with a slender pedicel of about 1-2 cm long. The calyx is five-toothed, divided, pubescent, and lanceolate. Corolla is hypocrateriform, pentalobed with 1 upper slightly

bigger lobe opposite to other 4 lobes. Corolla lobes are elliptic, white with pinkish throat and acute apex, comprising of narrow, cylindrical, pubescent corolla tube about 1.5-2 cm. Androecium encompasses 4 didynamous to subequal, exserted stamens, filiform, creamish white filaments, and bilobed, elliptic anthers. Gynoecium comprises of oblong, quadra-lobed, quadra-loculed ovary, filiform style and shortly 2-fid stigma. The plant produce metallic blue drupes of about 1-1.5 cm in diameter and shallow cupular, pinkish calyx. Fruits turn purplish-black in color upon ripening [10] **Fig. 1**.

FIG. 1: PLANT OF *C. INFORTUNATUM* L. SHOWING INFLORESCENCE AND FRUITS

Phytochemical Portrayal: The phytochemical make up of *C. infortunatum* has been widely discussed and determined by several groups from early times due to its undeniable ethnomedicinal values [11]. The foremost components accounted are triterpenes, flavonoids, saponins, steroids, alkaloids, lupeol, glycoside benzoic acid derivatives and ß-sitosterol, cholesterol, clerodolone, clerodone and proteins [12, 13, 14].

In 2017, Wang *et al.*, reviewed the presence of over 280 chemical constituents from different parts of plants belonging to genus *Clerodendrum*, cataloged as 58 diterpenoids, 43 flavonoid and flavonoid glycosides, 40 phenylethanoid glycosides, 43 steroids and steroid glycosides, 31 triterpenoids, 27 monoterpene and its derivatives, 13 cyclohexyl-ethanoids, 4 anthraquinones, 3 sesquiterpene, 2 cyanogenic glycosides [15]. Different plant parts have been advocated for diverse medicinal applications from ancient times and a glance into the chemical constituents of different plant parts individually gave a notion of the diversity in phytochemical composition. Reports point out aerial parts, roots, and leaves as the most abundant store-house of bioactive phytochemicals.

The leaves were narrated to contain a bitter principle, clerodin; saponins; glycerides of linoleic, oleic, stearic and lignoceric acids; sterols; triterpenes; tannin; glucuronide and gallic acid. The roots were stated to be rich in luperol, β-sitosterol, triterpenes, flavonoids such as cabruvin and quercetin[10]. Clerodin and hentriacontane has been found in flowers [16]. The seeds were reported to contain fatty oils like palmitic, oleic and linoleic acids [17].

The chemical constitution was conveyed to fluctuate in accordance with the solvents used for the extraction. The aqueous extracts were found to be loaded with alkaloids, phenols, anthraquinones, terpenoids, tannins, steroids, saponins, carbohydrates, glycosides and proteins. Extracts in methanol and ethanol presented the same chemical constitution except saponins. Ethanol extracts indicated the presence of flavonoids and triterpenes whereas, ethyl acetate extracts reported the presence of all these components except flavonoids, tannin and steroids [18]. Several groups round the world reported the presence of triterpenes *viz*, betulin and betulinic acid in the vegetative parts of *C. infortunatum* and many other Clerodendrone members [19, 20].

Betulinic acid (3β, hydroxy-lup-20(29)-en-28-oic acid), the pentacyclic triterpenoid, results from the oxidation of betulin (3β-lup-20(29)-en-3, 28-diol) **Fig. 2**. Both betulinic acid and betulin are present in the alcoholic extract of leaf and root of several *Clerodendron* species [19]. Recently, evidence of betulin has been reported from the alcohol extract of leaf and betulinic acid from the alcohol extract of the root of this plant [20].

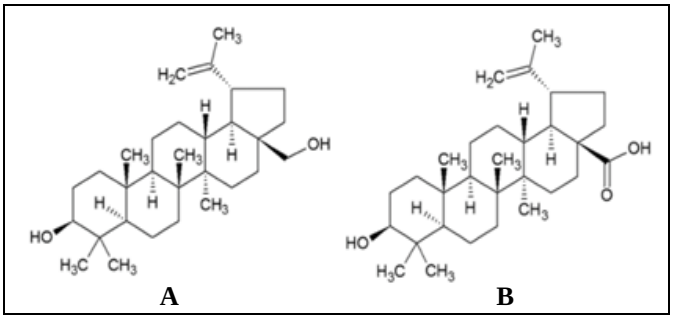

FIG. 2: CHEMICAL STRUCTURE OF BETULIN (A) AND BETULINIC ACID (B)

***C. infortunatum* – A Prodigious Treasure for Indian Folk Medicine:** The practice of putting in *C. infortunatum* in traditional medicine as an antibacterial, antifungal, analgesics [21], anti-helmentic, hepato-protective and anti-inflammatory agent [22, 23], in the treatment of bronchitis, asthma, epilepsy [24], fever, diseases of the blood, inflammation [25], burning sensation and tuberculosis dates back to ancient era [26]. Traditionally, among the Kuki and Rongmei Naga tribes of North-East India oral administration of leaf extract is being practiced for fever and bowel troubles [27]. Likewise, appending of fresh leaf juice rectally was carried out for eradication of ascaris, and leaves and flowers were said to be soothing scorpion sting [28]. Many tribes of North Bengal such as Rabha, Rajbanshi, Polia, and Lepcha have a custom of setting up fresh root bark for diarrhea. Leaf extracts is said to alleviate stomach pain and diabetes [29] by the Kachari, Hmar, and Riang tribes of Barak Valley and North- Cachar hills. The root paste is used as a bandage in swelling [30] and fresh leaf juice has been used as vermifuge and in the treatment of malaria [31].

Upshots of *Clerodendrum infortunatum* in Cancer: The perception of persuasive use in folk medicine and affluence of phytochemicals with diverse medicinal weightage in *C. infortunatum* extracts has given it an irrefutable echelon in modern chemotherapy. Many reports suggest the anticancer activity of leaf and root extracts using various solvents [32]. The anticancer potential of betulin and betulinic acid isolated from a variety of plants and its application in the treatment of many types of cancer by the traditional healers has been well documented. It has been reported that Swami Nirmalananda, a well-known traditional healer, has patented and practiced the application of *C. infortunatum* root extract in treating cancer. The report suggests the presence of a glycoprotein in the aqueous extract of the root, which confers the anti-cancer activity [33]. However, there are no further studies to substantiate the same. Traditional healers suggest the use of a decoction of the roots of *C. infortunatum* as a preventive measure for many of the cancers.

Cancer is a mysterious disease taking all possible routes for making a normal cell malignant. Hanahan and Weinberg (2011) [34] has reviewed the different hallmarks of cancer which has facilitated the oncologists in better understanding of tumor traits and untying novel trajectories in drug design. The hallmarks verbalize the different anti-cancer defense mechanisms orchestrated by cells which are amended during tumorigenesis. Self-reliance in growth signals and insensitivity to anti-growth signals are two major tumorigenic traits reported and have been supported by other features such as apoptotic evasion, infinite replicative potential, persistent angiogenesis, tissue invasion, and metastatic potential, immune evasion, genomic instability, and metabolic abnormality. A better understanding of these features and the effect of alteration of any of these in tumorigenesis is important in drug discovery and modernization of existing ones to improve therapy. Most of the phytomedicines are being focused in this point of view for being targeted to an anti-tumorous glory. The effect of these compounds in any one or combination of the above listed carcinogenic aspects is being analyzed for studying the anti-tumor potential of the compound. *Clerodendrum* extracts using different solvents are also possible candidates of scrutiny as anti-tumor agents due to its superfluity in medicinal phytochemicals.

Inhibition of Growth Signals and Immune Evasion: Many a number of phytochemicals reported as anti-tumorigenic till date is found to be capable of inhibiting the self-sufficiency in growth signals which is a vital characteristic attribute of cancer cell [35]. Nuclear transcription factor NFκB, a group of five proteins namely c-Rel, Rel A (p65), Rel B, NF-κB1 (p50 and p105), and NF-κB2 (p52) has been shown to regulate the expression of several genes whose products are known to play key roles in carcinogenesis[36]. Its signaling pathway has been renowned as a commander in many cancers in promoting tumour survival and maintenance, metastatic potential along with resistance to apoptosis [37]. Betulinic acid has been shown to inhibit the activation of nuclear factor-kappa B (NF-κB). NF-κB is stimulated by a variety of stimuli, such as lipopolysaccharide (LPS), cigarette smoke, tumor necrosis factor (TNF), interleukin (IL)-1, hydrogen peroxides, ceramide, ultraviolet light, phorbol myristate acetate (PMA), and okadaic acid (OA) *etc* [38]. Betulinic acid is reported to be an inhibitor of TNF-induced NF-κB activation [39].

Regulating the Infinite Replicative Potential and Angiogenesis: Several other mechanisms of tumor cell killing by betulinic acid has been reported. Chadalapaka *et al.,* (2010) [40] and Pathi *et al.,* (2011) [41] have acknowledged the inhibition of specificity protein (Sp) transcription factors, cyclin D1 and epidermal growth factor receptor (EGFR) involved in cell cycle progression and the angiogenic pathway. Reiner *et al.,* (2013) [42] have publicized that betulinic acid surges the degradation of cell cycle-associated proteins cyclins A, B1, D1; kinases such as Cdk1, 2, 4 and transcription factor E2F1in the prostate cancer cell line. Similar to campothecin, betulinic acid directly interacts and appreciably hinders the catalytic activity of mammalian type I DNA topoisomerase, by preventing the formation of a binary complex with DNA[43].

Regulating Tumor Invasion and Metastasis: EMT (Epithelial-Mesenchymal Transition) is a fundamental step in the metastatic cascade of tumor cells. Betulinic acid is reported to be inhibiting the metastatic potential of tumor cells by blocking the Epithelial-Mesenchymal Transition (EMT) pathway. Chen *et al.,* presented a drastic down-regulation of N-cadherin with upregulation of E-cadherin disabling the EMT process upon treatment with betulinic acid in gastric carcinoma cells [44]. Early in 2018, a comparable phenomenon has been stated in pancreatic carcinoma cells by Liankang Sun *et al.* [45]

Augmenting Apoptotic Execution: The cytotoxic activity of many of the natural products has been linked to their ability to trigger cell death pathways, mainly apoptosis. Apoptosis or self-inflicted cell death is a highly conserved intrinsic death program that plays a key role in maintaining tissue homeostasis and therapeutic execution. The ability of *C. infortunatum* root and leaf extracts to induce apoptosis in cancer cell lines and in animal models has been of great importance from early times. Fulda (2008) [46] has reported extensive research on the apoptotic potential of betulin and betulinic acid in cancer cell lines and animal models and highlights the two compounds as highly apoptotic, triggering mitochondrial (intrinsic) pathway of apoptosis. Betulin and betulinic acid-containing plant parts have been used in folk medicine for centuries [47]. The presence of these compounds is now confirmed in *C. infortunatum,* explaining the anti-neoplastic potential of the plant extract.

Tumor cells treated with betulin exhibited most of the characteristic and confirmative features of apoptosis *viz,* rounding of the cell, membrane blebbing, chromatin condensation, nuclear fragmentation, and formation of apoptotic bodies [48]. Apoptosis, in general, is mediated through two major signaling pathways: the extrinsic (death receptor) pathway and the intrinsic (mitochondrial) pathway. There are several reports demonstrating the ability of betulin to induce apoptosis in a variety of cancer cell lines [49,] and its efficacy has been found to vary in different types of cells.

Apoptosis was induced by betulin in different cancer cell lines such as A549, Jurkat, and HeLa by way of the mitochondria-mediated intrinsic pathway [50]. Potze *et al.,* revealed the progressive activation of caspase-9, -3, and -7, followed by the cleaving of poly (ADP-ribose) polymerase (PARP), pointing to the occurrence of caspase-related apoptosis [51]. As a result of betulin treatment caspase-8, the crucial modulator of the extrinsic pathway is kept inactive, and caspase-9, the switch of intrinsic pathway gets triggered, ensued by instant translocation of pro-apoptotic proteins—Bax and Bak to mitochondrial membrane bringing about release of cytochrome c and Smac, ending up in loss of mitochondrial membrane potential [50, 51].

The preliminary studies from our group to evaluate *in -vitro* cytotoxicity of *C. infortunatum* in a series of cell lines of different origin reinforces the high anticancer potential offered by the plant, which warrants further detailed analysis. The cytotoxicity of *C. infortunatum* has been verified in the extracts rooted out using different solvent systems in cell lines of diverse origins such as SiHa, C-33 A, MCF7, MDA-MB-231, A549, K-562, HCT116, A375, and HepG2 **Fig. 3**. Among the different solvent systems employed, ethyl acetate fractions rank first, displaying significant cytotoxicity for all the cell lines studied here. Reports suggest the betulinic acid-induced cytotoxicity of *C. infortunatum* extract to hormone receptor-positive breast cancer cell lines and cervical cancer cell line, though biochemical characterization of the active fraction of this plant requires further elaboration [32]. Betulinic acid has also been reported to upwell the

generation of reactive oxygen species (ROS) without the association of CD95 receptor/ligand or the wild-type p53 system signaling mitochondrial-mediated apoptosis [39, 49].

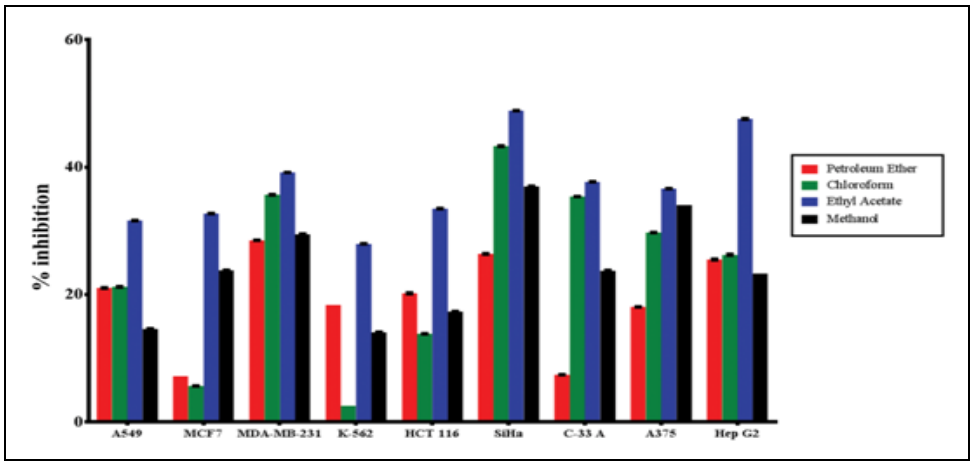

FIG. 3: CYTOTOXICITY OF *C. INFORTUNATUM* EXTRACTS IN A SERIES OF CANCER CELL LINES. Percentage inhibition displayed has been studied at 200µg/ml concentration of extracts rooted out using different solvent systems mentioned. The values are expressed as means ± SD of triplicate evaluates

Mutation of TP53 gene, which is considered as the "*guardian of genome*" has been observed in almost all types of cancers, with cervical and breast ranking top. Cervical cancers are characterized by the presence of oncogenic HPV and it is reported to exhibit p53 degradation mediated by HPV E6 protein in association with the cellular ubiquitination enzyme E6-AP (E6 associated protein) [52]. More than 80% of the triple-negative breast cancers also harbor p53 mutation [53]. Hence, anticancer agents that act out in cancer cells by p53 independent mechanisms will be appealing for chemotherapy. Betulinic acid forms an imperative entrant in this aspect [54]. Saeed *et al.*, have suggested that betulinic acid exerts cytotoxicity in tumor cells via targeting Autocrine Motility Receptor Factor [55].

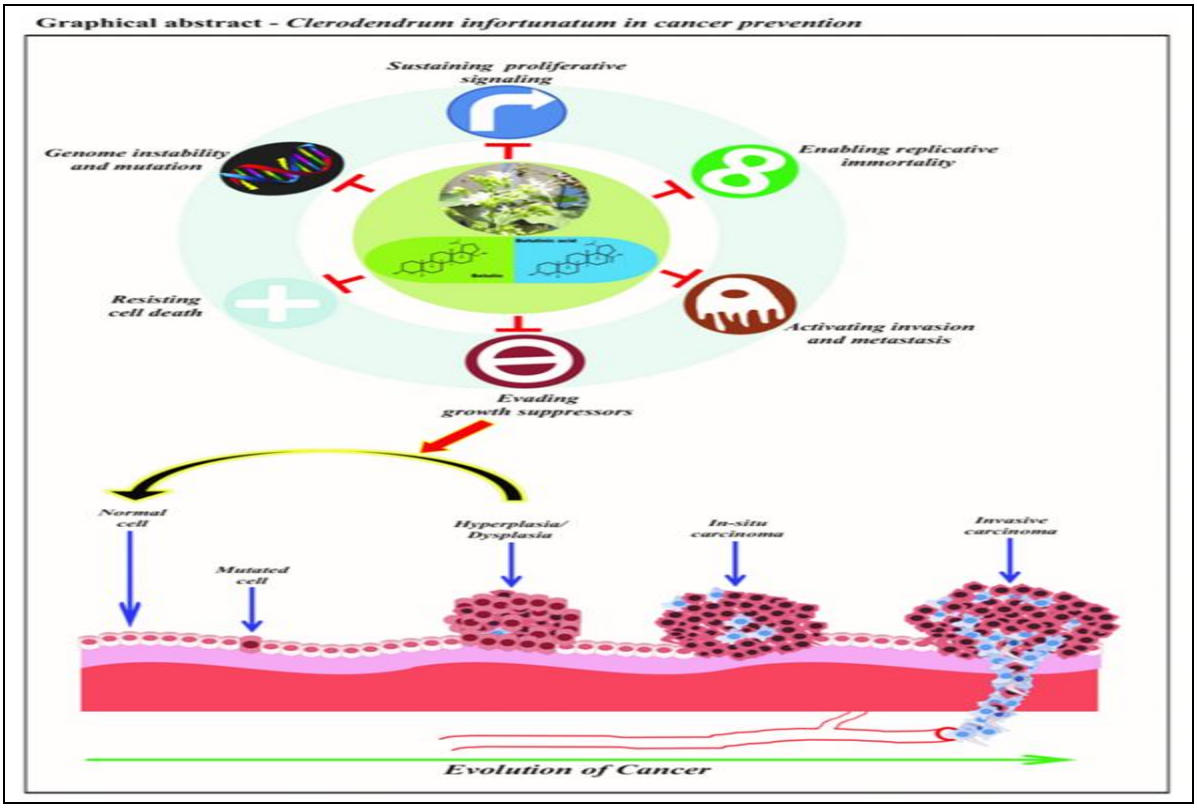

FIG. 4: SCHEMATIC REPRESENTATION OF THE MODEL PROPOSING THE CANCER PREVENTIVE POTENTIAL OF *CLERODENDRUM INFORTUNATUM* EXTRACTS AND ITS PHYTOCHEMICAL CONSTITUENTS

CONCLUSION:

***Clerodendrum infortunatum* – A Glory in Cancer Prevention:** Despite the enormous interest being devoted in cancer prevention and anticancer therapies in recent years, this disease continues to exhibit a high mortality rate and to hold back therapy owing to numerous side effects. Most of the cancers, particularly epithelial-derived ones, have a natural history of progression, evolving from hyperplasia to dysplasia to in-situ carcinoma/intraepithelial lesions and ultimately to an invasive tumor. The majority of the "Hallmarks of Cancer" is obvious in the premalignant conditions opening spectacular opportunities for chemoprevention if detected early. The articles reviewed here authenticate the anticancer potential of two pentacyclic lupane type triterpenoids, namely betulin and betulinic acid, bestowing in the leaves and roots of *C. infortunatum*. The compounds are considered to be strong inhibitors of sustaining growth signals and replicative immortality which is the key feature of carcinogenesis. The potential of these compounds to trigger apoptosis in cancer cells has also been confirmed in a broader panel of cell lines. The anti-metastatic potential of betulinic acid by inhibiting the process of EMT has also been established. Furthermore, several other properties like inhibition of tumor-associated neo-angiogenesis, migration of tumor cells *etc*., are also reported to be inhibiting tumor progression **Fig. 4**. It may be because of these properties of betulin and betulinic acid, present as major chemical constituents of *C. infortunatum* extract; the traditional healers suggest the decoction of it as a chemopreventive agent. However, the potential of this plant as a chemopreventive agent has to be further validated and reinforced in a finely honed manner.

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