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Bioactive Components of *piper betel* Could be Potential anticancer Agents: A short Review on Pre-clinical Inves-Tigations and Practical Challenges

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Abstract

The unmet treatment challenges such as intolerable adverse effects, massive immune suppression, and severe healthy tissue/organ toxicity with unaffordable treatment costs associated with conventional anticancer drug therapy have led to the exploration of complementary/ alternative strategies to control the out bursting cases of cancer. In this context, plant-derived bioactive components have been increasingly popular as effective therapeutic options for the treatment of cancer. Phyto bioactive components (PBCs) derived from *Piper betel* have been shown to possess useful immune-modulatory, antioxidant, anti-inflammatory properties both *in vitro* and *in vivo*. At present, a large volume of pre-clinical studies have documented the beneficial effects of *Piper betel*-derived PBCs in various cancer therapy, either alone or in combination with established chemo drugs. The present review aims to provide a comprehensive research data on the therapeutic effectiveness of PBCs of Piper betel against various cancers to establish its druggability. The review would be useful to provide essential evidence-based support for furthering work on large scale formulation development as well as future clinical studies of *Piper betel*.

Key words: *Piper betel,* bioactive components, Therapeutic potential, Cancer therapy

1. Introduction

Application of phyto bioactive components (PBCs) for the treatment of cancer has been one of the emerging trends in drug delivery research. In view of the unavoidable adverse effect of conventional anticancer drugs associated with immune suppression and healthy tissue toxicity, plant based pharmaceuticals are being explored heavily to ameliorate treatment outcomes in cancer therapy. Cancer is a typical pathological state, where the cellular reproduction process goes out of control with formation of abnormal mass of cells. Due to the result of DNA damage of cells, irregular growth and division are observed in the cancer cell. In the present world, cancer has been recognized as the second deadliest disease followed by cardiovascular disease (1). According to WHO cancer takes nearly 10 million life in 2020 only (2). Around the world, one in five men and one in six women during their lifetime develop cancer and one in eight men and one in eleven women died due to cancer (3). The existing conventional treatments, *viz*. chemotherapy, surgery, radiation in combination have been showing uncountable limitations, severe

adverse effects with negligible improvements in quality of life post treatment. Surgery/radiation also has limited role in cancer like leukaemia and lymphomas (4). Further, existing anticancer drug therapy with the present methodology destroys the tumour tissue with great accuracy but fails to distinguish between the healthy and tumour cells (5). All conventional chemotherapeutic medications are severely cytotoxic and have a low therapeutic range. Due to their extreme cytotoxicity, they affect the microtubule organisation and cell survival (6). From the current clinical practice data, it is established that the synthetic chemotherapeutic agents have less specificity to cancer cells which lead to several adverse effects. Because the anticancer drug targets actively developing cells, it also has negative effect on normal cells that grow rapidly such as the hair follicles, gastrointestinal tract, and bone marrow (7). To overcome these setback, plant-derived anticancer agents with less toxicity and more specificity is highly needed. There are many plants that have been used for the research of cancer treatment for many years. Among 35000 potential plant species, 3000 species showed desired therapeutic activity against cancer according to National Cancer Institute (NCI) (8). Betel leaf (*Piper betel*) is one of the common plants among them and is well-known for its various anti-oxidant, antimicrobial and anti-inflammatory properties (9). According to various researchers, PBCs present in *Piper betel* have selective toxicity towards cancer cells too. Recent studies have shown effective anticancer potential of *Piper betel* derived PBCs in ameliorating cancer both *in vitro* and *in vivo*.

Thus, objective of the present review is to provide updated information on the anticancer properties of *Piper betel* and its important phyto constituents on different cancers. Updated research works of pre-clinical studies involving *Piper betel* derived PBCs on various cancer cells have been included. Along with that, we have briefly covered the crucial challenges in the clinical translation or vulnerability of PBCs for industrial scale production. We believe the compiled reports on the anticancer activities of *Piper betel* would be helpful to provide useful insights in furthering research on its clinical aspects.

Betel leaf: Important bioactive constituents and traditional uses

Even in twenty-first century approximately 80 percent population in developing countries depends upon medicinal plant-based medicine as an affordable source (10). *Piper betel* (family: Piperaceae), a perennial, dioecious, evergreen, small shade-loving, aromatic root climber is one among Southeast Asia's most significant plants. In tropical and subtropical regions of the world this genus has been found largely distributed with wide range of traditional and medical applications (11). Betel vine is widely planted in Thailand, Sri Lanka, Malaysia, India, Nepal Taiwan, Pakistan, and other Southeast Asian nations (12).

From various studies on betel leaf, many biologically active components have been reported (11). Phenol is one of such important components present in the leaf. The unique strong pungent aromatic flavours of the leaf are due to the presence of phenol and terpene-like compounds. Various significant PBCs which are present in *Piper betel* include chavibetol (betel-phenol; 3-hydroxy-4-methoxyallylbenzene), chavicol (p-allyl-phenol; 4-allyl-phenol), estragole (p-allyl-anisole; 4-methoxyallylbenzene), eugenol (allylguaiacol; 4-hydroxy-3- methoxy-allylbenzene; 2-methoxy-4-allyl-phenol), methyl eugenol (eugenol methyl ether; 3, 4-dimethoxyallylbenzene), hydroxycatechol (2, 4-dihydroxyallylbenzene) etc. Along with these, caryophyllene, p-cymene, cadinene, eugenol methyl ether, γ-lactone, tritriacontane, dotriacontanoic acid, allyl catechol cepharadione A etc. are too found in the betel leaf in varying amounts (13).

Use of betel leaves in India has been documented in various old books and in Ayurvedic manuscripts. The use of betel leaves from 1400 BC was also evidenced in Vatsyayan's

Kamasutra in which aphrodisiac activity of betel leaves has been mentioned (14). Betel leaves are also used in several rituals in Southeast Asian nations such as India, Sri Lanka, and Bangladesh. Betel leaf has traditionally been used to cure problems such as itching, otorrhoea, traumas, mastoiditis, leucorrhoea, mastitis, headache, constipation gum swelling, rheumatism, wounds, and conjunctivitis (15). The wound healing properties are also identified from Indian traditional and conventional medical systems. Betel leave was recognized as a potent phyto medicine to assist the digestive process and shows a good effect for bronchitis treatment. Even it has traditional use as a flatus reliever to eradicate worms, bacteria. In India, betel leaf is very often chewed after meals, which shows moderate digestive stimulant activity (14). To cure cough, combination of *Piper betel* leaves and honey has been taken as a traditional herbal medication. Though, lots of medicinal effects of *Piper betel* were observed for several diseases from ancient times, but its therapeutic usefulness in cancer has been documented in twentieth century only (16).

Predicted mechanisms of Piper betel based PBCs for cancer prevention

Cancer is a typical disease and remains largely mysterious till today irrespective of eye-catching research progress in medical science. However, with the advancement of biotechnology, molecular engineering and pharmaceutical research, molecular insights of cancer progression is being unfolded slowly. In human bodies, free radicals in various forms such as reactive nitrogen species (RNS) and reactive oxygen species (ROS) are developed as a result of cellular metabolism. Excessive amounts of RNS/ROS lead to cytotoxicity, inflammation and even mutagenesis and thus have been identified as important molecular mechanism in cancer progression (17). *Piper betel* derived PBCs possess the ability to scavenge hydroxyl radical and superoxide radical. α, α-diphenyl-β-picryl hydrazyl (DPPH) radicals, superoxide radicals, and hydroxyl radicals have been found effectively scavenged by ethanolic and aqueous extracts of betel leaf (18). In a study on the antioxidant effect of ethanolic extract of betel leaf, a significant decrease in extracellular nitric oxide production was observed (19).

Eugenol, one of the key ingredients of betel leaf possesses strong antioxidant properties. In lipopolysaccharide-stimulated mouse macrophage cells, eugenol inhibited COX-2 gene expression, which eventually led to the suppression of inflammatory responses (20). Hepatic level of retinol, ascorbic acid (antioxidant molecules), glutathione, Superoxide dismutases (SODs) is an antioxidant enzyme was also found to be significantly increased by the *Piper betel* leaf extract as reported by Choudhary et al. (21).

Peroxidative attacks by free radicals can lead to the destruction of poly-unsaturated fatty acids present in cell membranes, leading to cell membrane dysfunction (22). In an *in vitro* examination on rat liver mitochondria, alcoholic extract of the betel leaf prevented lipid peroxidation. *Piper betel* derived PBCs have been found to enhance the amount of Glutathione S-transferases (GST), another key enzyme which protects the cells from the effect of toxic metabolites. This enzyme system too works to fight against various carcinogenic metabolites and mutagens (23). When laboratory mice were treated with *Piper betel* leaf extract and its individual components like α-tocopherol, β-carotene and hydroxychavicol, the amount of GST was found to be increased in their liver (14). Studies on the structure-based effects of acetylation on benzene ring hydroxyl groups have revealed the anti-nitrosating action of the molecule, which indicates their potential for antimutagenic activities. In a report, both hydroxychavicol and eugenol (two major PBCs in *Piper betel*) were found to decrease nitrosation in a dose-dependent manner *in vitro* (18). Predicted mechanisms of *Piper betel* and its bioactive constituents in cancer prevention/treatment have been depicted in **Figure 1**.

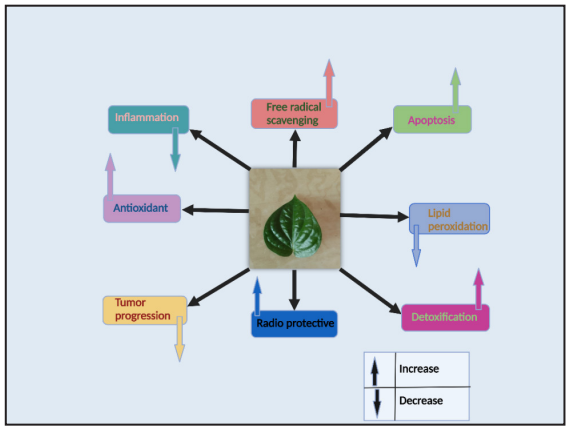

Figure 1.Mechanism of action of bioactive constituents of *Piper betel* in cancer prevention/ treatment

Recent research progress on Piper betel based PBCs in cancer

Many studies have documented the anticancer potential of *Piper betel* derived PBCs *in vitro* and *in vivo*. The *in vitro* anticancer activity of *Piper betel* leaves in KB cell line (oral squamous carcinoma) was tested in a recent study by Sadiya R Veettil et al. 2022. For the study, aqueous extract of the dried betel leaves was used. *In vitro* cytotoxicity experiment was conducted in a 96 well tissue culture plate and the plates were examined using an inverted phase contrast tissue culture microscope for 72 hours for any visible morphological alterations in cells. Cell viability percentage was determined using the MTT method. *Piper betel* leaf extract showed significant cytotoxicity in the tested KB cells as evidenced in the form of noticeable changes in cellular morphology like vacuolization of cytoplasm, rounding/granulation and cell shrinkage. The study overall demonstrated that increase in the quantity of leaf extract reduced the percentage of survival of KB cells (24).

Microtubule is an important part to maintain the cytoskeleton of cells. Microtubules contribute to shape, dynamics, movement of cells and thus are considered partly responsible for the cancer cell migration. Aqueous extract *Piper betel* leaf showed substantial reduction in cancer cell migration (A549 cells) and modulation in microtubule structure *in vitro* (25). To evaluate effectiveness of anti-migration effect, results obtained with the experimental leaf extract was compared with that of 5-fluorouracil (5-FU), an established anticancer drug. For the study, *Piper betel* leaf extract and 5-FU at two different concentrations were taken. When the results of the study were compared, it was shown that both betel leaf extract and 5-FU inhibited cell migration at low quantities. However, betel leaf extract at relatively higher concentration (100 g/mL) was significantly more effective against migration than 5-FU. The morphology, structure, and tubulin network of human colorectal adenocarcinoma cells (HT29) treated with *Piper betel* leaf extract, 5-FU, and paclitaxel were examined. Paclitaxel treated cells and *Piper betel* leaf extract treated cells both showed similar morphologies of round shaped cells with long distorted spindle. These spindles are defects on the microtubule which prevent cell division and lead to apoptosis. The study concluded that *Piper betel* leaf extract induced microtubule polymerization whereas at relatively low concentration, it inhibited cell migration (25). Thus, *Piper betel* derived PBC was found as potential microtubule-targeting agent with anti-migratory effects on cancer cells.

Antioxidant and anticancer properties of betel leaf extract was studied in MCF-7 human breast cancer cells (26). The antioxidant activity of betel leaves extract was shown by DPPH radical scavenging capacity. The SRB technique was used to analyse the cytotoxicity of betel leaf extract in MCF-7 cells cultured in Dulbecco's Modified Eagle Medium (DMEM). The cells were plated in a culture dish at 37°C for 24 hours and for 48 hours with different dosages of betel leaf extract to examine its cytotoxic and anti-migratory effect. MCF-7 cell survival was reduced as the dosage of *Piper betel* leaf extract was increased. It was also shown that the betel leaf extract reduced cancer cell migration in a concentration dependent manner. Following the reasonable cytotoxic and anti-migratory

effects of betel leaf extract on MCF-7 cells, its local application was considered. As a result, a transdermal patch containing *Piper betel* leaf extract was developed for application to the intended breast area (26).

Similarly, another study was conducted on the anticancer efficacy of silver nano bio-conjugates synthesized from the methanolic extract of the *Piper betel* leaf. In 10:90 ratio, the methanolic extract of betel leaf or 100µg diluted purified eugenol was added to 1 mmol silver nitrate solution followed by exposure to sunlight and centrifugation. The anticancer activity was compared among the silver nano bio-conjugate and with the raw material like betel leaf extract or eugenol (27). Oral cancer cells (KB) along with non-cancerous buccal cells were used for the study. Both the cells were seeded as 10^5 live cells/ ml for further experiments. In the cell medium, the silver nano bio-conjugate synthesised from methanolic extract of betel leaf as well as eugenol was added. Both cancerous and non-cancerous cells were tested for viability with the MTT reduction assay. Results of MTT assay indicated after exposure to betel leaf extract, eugenol, and the experimental silver nano bio-conjugates, KB cells exhibited a dose-dependent reduction of cell viability. As compared to their non-nano raw material counterparts, silver nano bio-conjugates had reduced viability. Results overall depicted the improved anticancer effects, when extract and eugenol get administered in silver nano bio-conjugates. However, the viability of healthy buccal cells was unaffected by different doses of silver nano bio-conjugates and eugenol, which means that silver nano bio-conjugates are not harmful to healthy cells. Apoptosis study further confirmed higher anti-apoptotic activity of the experimental silver nano bio-conjugates than plain extract/ eugenol. The nano bio-conjugates shifted cancer cells into S and G2/M phases, showing superior anticancer efficacy (27).

Methanolic extract of *Piper betel* leaf possessed antitumor efficacy against Ehrlich ascites carcinoma (EAC). The research was conducted in Swiss albino mice bearing EAC and the median survival study along with the life span of cancer induced mice was estimated (28). The EAC cells were transplanted intra-peritoneally in Swiss albino female mice. After 24 hours of transplantation of EAC cells, the methanolic extracts were administered in different doses, *viz*. 25, 50, 100 mg/kg body weight for 9 days, The antitumor effect of the extract and fractions were evaluated by cell study from the mice as like viable and non-viable tumor cell count, tumor volume packed cell count. Haematological and biochemical parameters including haemoglobin content, RBC and WBC count, serum biochemical serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), serum alkaline phosphatase (SALP), serum bilirubin, and total protein level were assessed. For antioxidant property, evaluation lipid peroxidation and catalase (CAT), reduced glutathione (GSH) and superoxide dismutase (SOD) levels were also calculated. The methanolic *Piper betel* leaf extract and 100 mg/kg body weight ethyl acetate fraction inhibited EAC cells significantly. Mice with EAC treated with betel leaf extract had a lower tumour volume, packed cells, and viable cell count, as well as a longer life time. Also, the haematological and serum biochemical profiles were found to remain in normal level as compared to EAC control mice. In case of methanolic extract and ethyl acetate fraction group, the lipid peroxidation get decreased and SOD, GSH, CAT levels were restored at normal level as compared to EAC control group. From the study, the antitumor effect of *Piper betel* leaf extract was well established (28).

Anti-carcinogenic properties of betel leaf extract was investigated by Toprani, R et al. in by using two different protocols in Swiss male mice. The effectiveness of Piper betel leaf extract against the standard carcinogen benzo[a] pyrene was studied in the first protocol using Wattenberg's stomach cancer model. *Piper betel* leaf extract was administered in eight weeks old male mice by intra-gastric instillation. In the second stage, effectiveness of *Piper betel*

leaf extract was determined against two tobacco-specific nitrosamines, N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino) -1- (3-pyridyl) -1- butanone (NNK). Nitrosamines were administered in mice's tongue along with oral administration of the betel leaf extract with drinking water. Two different doses were used for NNN and one dose for NNK. In the first protocol, *Piper betel* leaf extract showed the reduction of tumorigenic effect of benzo[a]pyrene in the fore stomach tumour to very noteworthy range. In case of second protocol, the betel leaf extract treatment reduced the mortality of the animals. But the long term studies showed statistical significant difference in decreasing tumor volume in between NNN treated and betel leaf extract treated groups. The study thus evidenced the anti-carcinogenic effect of betel leaf extract in vivo against benzo[a]pyrene. Betel leaf derived PBCs were involved to minimize the toxicity caused by NNN and NNK (29). Anticancer effectiveness of *Piper betel* derived PBCs was also reported against prostate cancer cells. In the experiment by Rutugandha P. et al. *Piper betel* leaf extract was found to possess effective anticancer potential in prostate cancer therapy *in vivo*. For the study, 6 weeks old male mice prostate cancer cells (PC-3-luc) were inserted subcutaneously. At three different doses, the *Piper betel* leaf extract were administered orally in three different groups of animals along with the control group. The result showed that *Piper betel* leaf extracts significantly inhibited the prostate cancer cells proliferation in mice. To identify the main PBCs in the tested betel leaf extract, classical column chromatography was performed using solvents of different polarity strengths followed by thin layer chromatography. Among the fractions, F2 showed better *in vitro* effectiveness to inhibit prostate cancer proliferation almost three times than other treatment groups. Further, the F2 fraction was subjected to nuclear magnetic resonance analysis, mass spectrometry, and high-performance liquid chromatography, which confirmed that phenols, chavibetols (CHV) and hydroxychavicols (HC) were the principal PBCs. HC containing sub-fraction was eight times more potent for inhibition of prostate cancer proliferation as compared to CHV containing sub-fraction. The study thus concluded that perhaps HC is a major component in *Piper betel* for the potential candidate of prostate cancer treatment (30). Anti-oxidant potential of *Piper betel* leaf extract was used to reduce growth of MCF-7 cells (31). For the determination of flavonoid and phenolic content of the leaf, colorimetric assay was used. To analyse the antioxidant activities of the plant extracts various assays like DPPH, FRAP, nitric oxide, superoxide anion and hydroxyl radical scavenging assays were used. The cell viability test was carried out using the MTT assay methods, with MCF-7 cancer cells on 96 well culture plates. After 24 h, the leaf extracts at various concentrations were added in each well. Among the tested extracts, ethyl acetate extract showed higher ferric reducing and free radical scavenging activity when measured with nitric oxide radicals, superoxide anion and DPPH. In case of hydroxyl radical scavenging activity it is second highest, just after aqueous extract. Pearson correlation analysis revealed no significant relationship between phenolic content and hydroxyl radical scavenging ability. Among all the betel leaf extract the phenolic contain is maximum in ethyl acetate extract, even three times higher than hexane and sixteen times higher than methanol extract. But flavonoid amount is highest in methanolic extract. However, mostly the hexane and ethyl acetate extracts showed effective dose-dependent inhibition in the cytotoxicity assay against MCF-7 cells, with IC_{50} values of 65.00 ± 0.00 and 163.30 ± 2.89 g/ml, respectively (32). SOD and catalase activity were enhanced in MCF-7 cells treated with ethyl acetate fraction. The work in a nutshell overall depicted potential antioxidant and anti-proliferative activity of ethyl acetate fraction of betel leaf, which could be further investigated for further clinical feasibility.

A list of recently conducted research on *Piper betel* and its PBCs on various cancers has been depicted in **Table 1**.

Table 1 A list of recently conducted research on Piper betel and its PBCs on various cancers has been depicted

S . no	Form of formulation and used constituents	Type of cancercancer cell /carcinogens	Result	Reference
1	*Piper betel* leaf extract	Tobacco induced carcinogenesis (NNN , NNK)	The constituents of betel leaf reduce the toxicity instigated by NNN and NNK.	Bhisey, R.A., at al. (2012)
2	*Piper betel* leaf extract eugenol, hydroxychavicol. -carotene and -tocopherol	bhide	Betel leaf extract like hydroxychavicol, -carotene, -tocopherol, eugenol, all significantly reduced the tumor growth. -carotene and -tocopherol show intense protection even in lower concentrations.	Gupta, R.K., at al. (2022)
3	*Piper betel* leaf extract with water, methanol, ethyl acetate, hexane	Breast cancer (MCF-7)	Ethyl acetate extracts showed maximum inhibition of proliferation against the MCF-7 cell	Abrahim at al. (2012)
4	Transdermal patch with *Piper betel* leaf extract	Breast cancer (MCF-7)	Transdermal patch shows prolonged anticancer effect compared to the leaf extract.	Boontha at al. (2019)
5	*Piper betel* leaf extract	Prostate cancer	Piper betel leaf extracts significantly inhibit the human prostate implanted in mice. Hydroxychavicol is a major component in *Piper betel* for the potential candidate of prostate cancer treatment	Paranjpe at al. (2013)
6	*Piper betel* leaf extract	Oral cancer (KB cell)	With the increase of the *Piper betel* leaf extract the cytotoxicity of KB cells also get increased.	Veettil at al. (2022)
7	Piper betel leaf methanolic extract and eugenol were used to create silver nanobioconjugates.	Oral cancer (KB cell)	The conjugated silver nano form shows higher anticancer properties compared to the respective unconjugated form. And silvenano bio conjugate are not cytotoxic for healthy cells.	Preethi at al. (2016)
8	Hydroxychavicol	Oral cancer (KB cell)	Hydroxichavicol promotes the inhibition of cell cycle, growth of KB cell, leads to apoptosis of KB cell	Chang at al. (2002)
9	Methanolic*Piper betel* leaf extract	Ehrlich ascites carcinoma (EAC)	Mice with EAC that were given betel leaf extract had a reduced tumour volume, packed cells, and viable cell count, as well as a longer lifetime.	Alam at al. (2015)
10	Hydroxychavicol	pancreatic cancer	Hydroxychavicol produced DNA damage, which caused pancreatic cancer cells to apoptosis.	Majumdar at al. (2019)

Challenges

Undoubtedly, emergence of phyto active components has boosted cancer research. As we discussed, multiple options are available for the fabrication of betel oil based PBCs with modified physiochemical characteristics. However, apart from the huge benefits that the phyto-medicine offers, there still exist many uncleared problems on their way for clinical application. Large scale synthesis, regulatory clearance followed by commercialization of such PBCs-based medicines need long term research collaboration with time-bound vision by pharmaceutical companies. Careful analysis of biocompatibility, therapeutic potential, structural stability, in vivo life span, biodistribution profile in healthy organs/tissues should be conducted along with long-term toxicity analysis (36). Though, many times, the formulation technologists and academic scientists argue that usually PBCs possess no/negligible side effects or toxicity profile as they belong to herbal origin. But, this argument clearly lacks scientific merit as no such regulatory bodies will ever accept this. Merely an herbal origin tag does not certify a component to be non-toxic or safe for human application. Also, the regulatory procedures are not streamlined in between Allopathic and Homoeopathic/Ayurvedic medicine systems. Thus, formulation of PBCs must pass through toxicity testing protocol and must ensure its safty profile to get nod for commercial approval.

Another striking issue that is associated with PBCs is their versatile availability and yield percentage of active components. In many cases, the yield amount of active component remains too low from the plant raw materials used for extraction. Geographical distribution of the plant may vary, which also affects their active principles and contents. Many times, the low yield coupled with presence of variable active components in the plant material is not being able to meet the demand. In case of *Piper betel*, if we consider, then the yield percentage of essential oil from its leaves remains maximum up to 2 % w/v. However, this might vary from species to species and largely depend on the geographical location. These factors also need to be considered for phyto fabrication. If the desired quantities of PBCs are not up to the mark, its proper way of plantation need to be planned, which ultimately would further add to the final cost of therapy. The extraction procedure or isolation of PBCs also needs up gradation with utilization of cutting-edge tools and flexible designs.

Despite eye-catching research advancements in drug delivery arena, use of phyto pharmaceuticals in novel delivery platforms stands a long way from clinical translation. Low drug loading capacity of nanocarriers along with stability issues of PBCs still an unsolved issue. Ligand-modified tailored nanocarriers though have put some promising clue for targeting of cancer, but such approach is yet to find its way for PBCs. The main reason is still the stability problem during manufacturing, and long term storage. Insufficient data are available till now on the in vivo efficacy of tailored nanocarriers loaded with PBCs over the plain nanocarrier formulations or the marketed conventional formulations for the treatment of cancer. Improved efficacy of PBCs loaded nanocarriers over conventional drugs has still remained marginal in pre-clinical study reports.

As discuseed before, large scale manufacturing of PBCs remains a key issue, as pharmaceutical companies hesitate to invest in them. Irrespective of voluminous in vitro/in vivo reports on the different phytopharmaceuticals at academic level, they yet to see day light at technology transfer. Lack of well-designed, optimized manufacturing procedure, standardized processing steps, improvement in material yield hijacks the transition from laboratory to industrial scale. For, pharma-companies, all therapeutic outcome claimed at in vivo stage are immaterial unless the clinical benefit is guaranteed.

Few specific points need to be considered seriously to avail the Piper betel-derived PBCs at bed side (37, 38).

a) Careful design and engineering of large scale

manufacturing process.

b) Toxicity analysis of PBCs-loaded carriers

c) In vitro/ in vivo correlation analysis

d) Continuous exchange of ideas between industry and academic scientists

e) Designing of collaborative research work between leading research laboratories considering the regulatory guidelines

Conclusion

It is an accepted fact that novel technology holds the potential to improve the therapeutic effectiveness of PBCs in cancer therapy. With the use of hyphenated technologies, advanced biomaterials, and well-designed formulation protocols, PBCs-based therapeutics would see day light in coming days. Use of *Piper betel* derived PBCs for the treatment of cancer is attracting attention of formulation scientists in recent days. It is quite evident that *Piper betel* and its constituents have a remarkable prospective to fight against breast cancer, oral cancer, prostate cancer. However, like the usual problems associated with clinical translation of other PBCs, further pre-clinical studies are too are highly warranted for *Piper betel* based therapeutics. In terms of biocompatibility, easy availability, safety profile etc. *Piper betel* derived PBCs could stand differently. Its wide range of availability across the geographical locations in India and long history of traditional uses could pave its patient compliance. Further investigations on the anticancer effectiveness of *Piper betel*-PBCs would help it to emerge as an effective alternative or complementary medicine for cancer application, which would in turn motivate the farmers for its wider cultivation. In many parts of India including Odisha, the large scale cultivation of the *Piper betel* would promote the socioeconomic status of the regions too. In a nut shell, *Piper betel*-PBCs based nanocarriers still have to pass through a long journey to find them in clinical stage as alternative treatment strategy for cancer. However, with advancement of technological innovations and collaborative research strategies would make the challenges to be conquered in future.

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Disclosure statement

The authors of the article have no conflict of interest to declare.

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