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Biogenic Silver Nanoparticles from *Pogostemon cablin* Benth. for Cancer Therapy: A review of phytochemistry, green synthesis, and anticancer potential

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Abstract

Chemotherapy has two problems that have not yet been fully addressed: it does not distinguish tumor cells from healthy cells effectively, and tumors can adapt to it. Plant extract-based silver nanoparticles have been proposed as an alternative, and several have shown activity against cancer cell lines. *Pogostemon cablin* Benth., a plant known as nilam in Indonesia, fits this profile but has rarely been studied in this context. Its leaves contain patchouli alcohol, pogostone, and a long list of flavonoids and phenolic acids, and the crude extract alone has been shown to reduce the viability of leukemia, colorectal, and endometrial cancer cells. A method for turning patchouli leaf extract into silver nanoparticles exists, though it was built for an antibacterial wound dressing rather than for cancer treatment. However, no one has the obvious next step and tested these nanoparticles against tumor cell lines. This review works through what discusses plant chemistry, the general procedure of green nanoparticle synthesis, the characteristics of these particles tend to look like once they are characterized, the efficacy of plant-based nanoparticles in killing cancer cells, and the current safety data, mainly to clarify the existing gaps.

Keywords: Anticancer; Cervical cancer; Green synthesis; *Pogostemon cablin* Benth.; Silver nanoparticles

1. Introduction

In 2022, approximately 20 million people were diagnosed with cancer, and around 9.7 million died [1]. Cervical cancer accounted for a significant part of that, with approximately 662,000 new cases and 349,000 deaths, making it the fourth most common cancer in terms of both incidence and mortality among women worldwide. Surgery, radiotherapy, and chemotherapy are the main treatment modalities, which are mixed and matched depending on disease progression [1,2]. The basic flaw of chemotherapy has not yet been addressed. It cannot distinguish a fast-dividing cancer cell from a fast-dividing healthy cell; therefore, the usual list of side effects, such as hair loss, nausea, and a weakened immune system, comes bundled with the treatment, almost by design and tumors adapt [3]. A regimen that works well in the first cycle can lose its effect by the third cycle, which is a large part of why relapse remains a common outcome in patients with ALL [4]. None of this is new. Nanomedicine has been proposed as a solution to this problem [5,6].

Nanoparticles measure between 1 and 100 nm in size [7]. At this scale, the surface area relative to volume becomes large, and cells take up the particles far more easily than they would anything larger [8]. Therefore, nanoparticles have been used in drug delivery, imaging, and direct cancer cell killing applications [9,10]. Therefore, the particle formation method is crucial in this regard. Chemical reduction and physical routes, such as laser ablation, can provide tight control over particle size, but usually at the cost of toxic reagents or a lot of energy, and the finished product is not always tolerated well by living cells. [11]. Green synthesis circumvents many of these issues by using biomolecules already present in plants or microbes for reduction and stabilization, instead of synthetic chemicals [12]. In several side-by-side

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comparisons, nanoparticles made this way have been found to be less toxic to normal cells than their chemically synthesized counterparts [8,9]. This is a significant reason why this method was adopted in the present study.

Plants are usually the preferred source over bacteria or fungi, mostly because they reduce metal ions faster and do not require sterile culture upkeep; therefore, scaling up the process is simpler in plants than in other organisms [12]. Several plant-based silver nanoparticles (AgNPs) have been shown to kill cancer cells [13,14]. AgNPs from *Ginkgo biloba* induced apoptosis in cervical cancer cells through the mitochondrial pathway, while AgNPs from *Nepeta deflersiana* induced similar effects in HeLa cells by increasing reactive oxygen species [5,6]. *Pogostemon cablin* has received far less attention, despite its crude extract showing activity against colorectal cancer, acute myeloid leukemia, and endometrial cancer cells in three unconnected studies [15,16,17]. More than 140 compounds have been identified in this plant [18]. Indonesia also supplies approximately 90 percent of the world's patchouli oil; therefore, unlike many candidate plants, the raw material here is neither rare nor costly [19].

One study has already made AgNPs from patchouli leaf extract, though for an antibacterial hydrogel film rather than anything to do with cancer [20]. To the best of our knowledge, no one has performed this synthesis and run it against the tumor cell lines. This review aims to bridge the gap between the solid anticancer chemistry of plant extracts and the application of nanoparticle protocols, as no previous study has done so [15,16,17,20]. The following sections cover the phytochemistry of the plant, the mechanism of green synthesis, the characterization data usually obtained for systems like this, the comparability of AgNPs in killing cancer cells, and the current status of safety evidence.

2. Botany and Phytochemistry of *Pogostemon cablin* Benth.

Pogostemon cablin Benth. is a member of the mint family (Lamiaceae) [18,19]. It is bushy and heavily branched, with soft hairy stems and small pink-white flowers, and is native to Indonesia, Malaysia, and the Philippines. Cultivation has spread well beyond that since then, but Indonesia still produces close to 90 percent of the world's patchouli oil, most of it from Sumatra and Sulawesi, where the growing conditions, loose humus-rich loam, a pH of approximately 5.5 to 7.5, warm and humid weather, and steady year-round rainfall, suit the plant well [19]. A recent review from the Department of Biology at Institut Teknologi Sepuluh Nopember examined the current status of in vitro propagation of patchouli alongside its pharmacology and pointed out that tissue culture can provide a more uniform planting stock than field cultivation [21].

Plants are chemically dense entities. To date, over 140 compounds have been identified, including terpenoids, phytosterols, flavonoids, organic acids, lignins, alkaloids, and several alcohols [18]. Patchouli alcohol has received the most commercial attention as it doubles as a quality marker in the essential oil trade [18,19]. However, pogostone, α-bulnesene, and seychellene are also consistently present in essential oils [18]. Neither of the two major markers was evenly distributed throughout the plant. In one analysis, pogostone was measured at approximately 31 percent in the stem and 21 percent in the leaf, whereas patchouli alcohol was measured at approximately 38 percent in the leaf and 10 percent in the stem [18]. This is not merely a taxonomic footnote but a significant finding. This is important for nanoparticle synthesis, as the tissue used for extraction determines the reducing and capping agents. The profile is also not fixed. Patchouli grown in vitro and treated with methyl jasmonate, a standard plant elicitor, showed a measurably different phytochemical composition and higher expression of *PatAACT*, a gene in the terpenoid pathway that eventually produces patchouli alcohol, compared to untreated plants [22]. This is noteworthy because it indicates that the reducing agent pool used for nanoparticle synthesis is not constant. In theory, it can be shaped upstream by the way the plant is grown before any extract is made [21,22].

The crude extract exhibited anticancer activity without the need for nanoparticles. In HL-60 leukemia cells, it slowed proliferation in a dose- and time-dependent manner, stopped the cell cycle at G0/G1, and induced apoptosis [15]. A separate study on colorectal cancer, conducted in both cultured cells and a mouse xenograft, tied the effect to higher p53 and p21 expression and lower cyclin-dependent kinase activity [16]. In endometrial cancer cells, an aqueous extract triggers apoptosis through caspase-3, caspase-9, and apoptosis-inducing factor (AIF) pathways [17]. Three cancer types, three separate groups, and roughly the same results each time [15,16,17]. This repetition is the whole argument for going further and putting this extract into nanoparticle form, since the crude extract by itself still runs into the usual bioavailability problems that limit most plant compounds before they get anywhere near clinical use.

3. Green Synthesis of Nanoparticles from Patchouli Leaf Extract

The chemistry is not complicated. Phytochemicals in the extract donate electrons to the metal ions in solution, reducing them to their metallic forms [23,24]. The same molecules generally remain attached to the particle surface as capping

layers, preventing agglomeration [5,6]. Phenolics and flavonoids perform most of the reducing work because their hydroxyl groups easily release electrons [18,23,24]. Compared with laser ablation on the physical side or chemical reduction using sodium borohydride, plant-based synthesis has one clear advantage: it is a single-step process that occurs at mild temperatures and does not involve hazardous materials [12].

A previously published protocol was used to synthesize patchouli. Khairan et al. prepared aqueous and methanolic leaf extracts and used them to reduce silver nitrate, and then built the resulting nanoparticles into a polyvinyl alcohol/corn starch/patchouli oil hydrogel for wound care [20]. Nanoparticle formation was confirmed, and the finished film showed antibacterial activity [20]; however, the particle size, shape, and zeta potential of the AgNPs on their own, apart from the film, were not reported. This is a real gap when attempting to compare this study with the rest of the plant-mediated AgNP literature, where these numbers are usually reported [23,24,25].

The same ITS Biology group that documented the effect of methyl jasmonate on patchouli phytochemistry [22] also studied elicitation in other medicinal plants. In *Gynura pseudochina*, another Southeast Asian traditional medicinal species, methyl jasmonate treatment during in vitro micropropagation stimulated growth and upregulated the expression of the phenylalanine ammonia-lyase (*PAL*) gene, a key step in the biosynthetic pathway leading to flavonoid production [26]. This is a different line of research from leaf extract-to-nanoparticle synthesis, focused on the chemical elicitation of intact plant tissue rather than nanoparticle fabrication from harvested extract, but it reinforces a point worth keeping in mind: the phytochemical output of a plant is not fixed and can be deliberately shifted through elicitation before extraction [22,26], whether the goal is boosting a target secondary metabolite or, as in the context of Chapter 3, optimizing the reducing and capping agent pool available for nanoparticle synthesis.

Beyond the existing protocol, the usual synthesis variables, such as extract concentration, silver nitrate concentration, temperature, pH, and reaction time, would presumably shape the particle size and morphology of *P. cablin*-AgNPs in the same way they do in nearly every other plant-mediated system [23,24]; however, none of these factors have been specifically studied for this species [20]. Silver is not the only metal that can be used for this purpose. The same phytochemicals that reduce Ag^+ should, in principle, perform the same function on other metal precursors; therefore, zinc oxide or gold nanoparticles from patchouli extract are options that have not yet been explored [18,20].

4. Physicochemical Characterization

No single instrument can provide a complete characterization of nanoparticles [8,9,11]. UV-Vis spectroscopy is usually the first check, picking up the surface plasmon resonance band that AgNPs typically show between 400 and 450 nm. TEM or SEM provides an actual image of the shape and dry-state size [27,28]. DLS and zeta potential describe the behavior of particles suspended in water [24,25]. FTIR spectroscopy was used to identify the functional groups involved in capping [23,24]. XRD confirmed the crystal structure, which is usually face-centered cubic for metallic silver [27,28]. Taken together, these give a reasonably complete picture; taken alone, any one of them leaves obvious gaps in the analysis.

Across studies that report all five, a fairly consistent size and shape pattern is observed: mostly 20–40 nm, spherical, and face-centered cubic (FCC) structures. [27,28]. *Nepeta deflersiana*-AgNPs was approximately 33 nm [6], *Tridax procumbens*-AgNPs was more widely spread, ranging from approximately 11 to 45 nm [25]. The zeta potentials varied significantly between the samples. *Tridax procumbens*-AgNPs sat at −20.7 mV, only moderately stable, while *Ginkgo biloba*-AgNPs reached a sturdier −34.56 mV [5,25]. This gap is probably due to the phytochemicals provided by each plant as capping agents rather than any other factor related to the silver core size. None of these five parameters have been reported for *P. cablin*-AgNPs separate from the hydrogel matrix in the existing study [20]; therefore, there is currently no way to determine where patchouli-derived particles would lie within this range. Filling in the basic characterization data is probably the most immediate next step before any biological testing can be confidently interpreted.

5. In Vitro Cytotoxic Activity Against Cancer Cells

The MTT assay remains the default method for testing whether AgNPs kill cancer cells in vitro [27,29]. Live cells reduce yellow tetrazolium salt into purple formazan crystals, and the resulting color is spectrophotometrically read as a surrogate marker of cell viability [28,30]. Since this reduction can sometimes reflect a shift in metabolism rather than cell death itself, a second assay is often run alongside it, with neutral red uptake being a common choice for checking lysosomal membrane integrity [31]. Once the dose-response numbers are obtained, fitting them to a four-parameter

logistic curve through nonlinear regression provides a better IC_{50} estimate than linear interpolation or the older probit method, mostly because the underlying curve is sigmoidal rather than linear [32].

HeLa is probably the most used cervical cancer cell line in the literature, and the reported IC_{50} values for plant-based AgNPs against it vary widely depending on the plant source [27,29]. *Nepeta deflersiana*-AgNPs induced clear dose-dependent apoptosis and necrosis in HeLa cells, with an increase in ROS levels and a decrease in mitochondrial membrane potential dropping alongside it [6]. *Ginkgo biloba*-AgNPs had a comparable effect on both HeLa and SiHa lines; the share of apoptotic HeLa cells increased from approximately 6.6 percent at baseline to nearly 44 percent at the highest dose tested [5]. The reason for the potency varying so much from plant to plant is not fully understood, but the particle size, which phytochemicals are doing the capping, and how quickly silver ions leach out of the particle all seem to matter, probably together rather than any one of them alone [25,27,29]. This is roughly the range in which any future *P. cablin*-AgNP result would need to be interpreted.

This activity is not limited to cervical cancer. Plant-based AgNPs have also shown cytotoxicity against breast cancer and leukemia cell lines, indicating a broad mechanism rather than one associated with a specific cell type [28,30]. Patchouli crude extract inhibits HL-60 leukemia cells and drives them into G0/G1 arrest [15]. Considering the antibacterial activity already confirmed for *P. cablin*-AgNPs [20], there is a strong case for testing these particles directly against HeLa or similar cells in future studies to confirm their safety [33].

6. Molecular Mechanisms of Anticancer Activity

Most plant-based AgNP studies have reported a similar mechanism: the particles enter the cell, reactive oxygen species accumulate, the mitochondrial membrane is destabilized, and the intrinsic apoptotic pathway is activated [5,6]. In cervical cancer cells, *Ginkgo biloba*-AgNPs lowered mitochondrial cytochrome C and increased cytosolic cytochrome C levels in both HeLa and SiHa cells, which activated caspase-9 and caspase-3 in a dose-dependent manner [5]. Cell cycle arrest tends to occur alongside this, usually in the G0/G1 or SubG1 phase [34]. *Nepeta deflersiana*-AgNPs arrested HeLa cells at SubG1, whereas ROS and lipid peroxidation increased and glutathione decreased [6].

This closely aligns with the effects of *P. cablin* crude extract alone without nanoparticles. In HL-60 cells, the extract also induced G0/G1 arrest, which was associated with reduced phospho-Rb and increased p21 levels, along with a broader decrease in cell cycle regulator protein levels [15]. Whether *P. cablin*-AgNPs would combine the standard ROS-mitochondrial route [5,6] with something extra from the plant's own compounds, particularly patchouli alcohol, given its independent cell cycle effects in the extract form [15,18], is a fair question but has not yet been tested. This hypothesis is worth pursuing and is not a finding that can be cited in future research.

7. In Vivo Evidence and Translational Potential

In vivo data for plant-based AgNPs lag well behind the cell-culture literature in general, and for *P. cablin*-AgNPs specifically there is none. We have evidence that the crude extract still works in a live animal: the colorectal cancer study cited earlier ran a mouse xenograft alongside its cell culture work, and tumor growth was suppressed. Therefore, the active compounds of plants are not just doing something in a dish [16]. However, this does not directly indicate how the nanoparticles would behave in vivo. Biogenic AgNPs from other plants have shown fairly low toxicity to healthy tissues in early in vivo safety checks, which supports the general biocompatibility argument for green synthesis, although not specifically for patchouli [33]. However, the in vivo studies using *P. cablin*-AgNPs remain unanswered [20,33].

8. Biosafety and Toxicity Considerations

Any anticancer claim must be weighed against how the material affects normal cells, and this is where the *P. cablin*-AgNP literature has the least to offer. Plant-based AgNPs tend to be gentler on healthy cells than chemically synthesized AgNPs, which is a large part of the selectivity argument for green synthesis [35]; however, this has not yet been verified in patchouli cells [20]. Hossain et al. found that their biogenic AgNPs barely touched healthy human peripheral lymphocytes while still working against bacteria and cancer cells [33]. A future *P. cablin*-AgNP study should show something similar before the material can be considered a therapeutic candidate [20,35]. At the very least, a proper selectivity index, IC_{50} in cancer cells set against IC_{50} in matched normal cells, plus some preliminary in vivo toxicology data, is the baseline that is still lacking in the literature.

9. Research Gaps and Future Directions

Taken together, these gaps are specific rather than vague in nature. No one has tested *P. cablin*-derived AgNPs against a cancer cell line, even with a working synthesis protocol on record [20] and solid anticancer data for the crude extract [15,16,17]. The basic characterization, size, shape, zeta potential, FTIR, and crystal structure have not been reported for these nanoparticles apart from the hydrogel matrix they were originally built into [20]. However, no study has examined the ROS levels, apoptotic protein expression, or cell cycle changes in cancer cells exposed to these compounds. No in vivo tumor data or dedicated safety studies are available for this drug. Elicitation methods that have already been shown to shift *P. cablin*'s phytochemical output, including methyl jasmonate treatment [22], have not been tested for their effect on nanoparticle synthesis efficiency or particle properties downstream, even though this connection follows fairly naturally from work already underway in the same research group [21,22]. The synthesis of other metals, such as zinc oxide or gold, from the same extract and a comparison of their potency against silver have not yet been attempted [20]. A study that works through synthesis optimization, full characterization, in vitro cytotoxicity, mechanism, and safety in sequence would close most of these gaps at once and would be a genuinely original contribution, given the limited research on this plant to date.

10. Conclusion

Patchouli has several advantages: well-documented chemistry, confirmed anticancer activity across three unrelated cancer types in the extract form, a working nanoparticle synthesis protocol, and a raw material supply that is largely controlled by Indonesia. However, to the best of our knowledge, no study has linked patchouli-derived nanoparticles to cancer cell activity. This review aims to bridge this gap by presenting sufficient evidence from comparable plant-based AgNP systems, addressing the missing piece, and testing *P. cablin*-AgNPs directly against cancer cells, which is a specific and well-defined experiment with *P. cablin*-AgNPs against cancer cells. This involves optimizing the synthesis, proper characterization of the particles, conducting standard cytotoxicity and mechanism assays, and eventually moving into animal models and safety testing, all of which are performed on this plant specifically, rather than being borrowed from its relatives.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article

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