Green synthesis of gold nanoparticles using plant products and plants extracts aiming for cancer therapy: helping the beauty to beat ‘cure’ the beast

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ABSTRACT
Since there is a noticed paucity in manuscripts exploiting the green synthesis methods in the preparation of gold nanoparticles, hence this editorial is introduced in order to encourage the researchers to more focussing on this topic. Brief demonstration of the different conducted green methods, examples of used plants and plants extracts and novel advanced methods such as the one-step synthesis of gold-coated polypyrrole photothermal nanoparticles and their use in cancer therapy are introduced.

Editorial
The gold nanoparticles are recently gaining more grounds in combating cancer. Recently, these colloidal nanoparticulate systems are exploited in photo-thermal therapy and as carriers for drug and anti-cancer molecules [1]. The application of these metal nanoparticles in cancer diagnostics and therapeutics is ascribed to their favourable optical and physical properties that offer a new platform for developing a cancer theranostic agent. The optical properties of gold nanoparticles are attributed to the surface plasmon resonance (SPR) phenomenon. SPR is considered a process where the gold electrons resonate as a response to an incident radiation. This causes the electrons to absorb and scatter the light as well. In this context, specifically-tailored gold nanoparticles were found to possess photon capture cross sections with a four to five magnitudes larger than those of the traditional photothermal dyes. These properties were exploited to obtain localized heating either to destroy cancer cells or for controlling the drug release for therapeutic purposes. Furthermore, the gold nanoparticles enjoy significant tuneable properties. This helps in obtaining nanoparticles of specific size and definite shapes and results in a plasmonic resonance shift from 520 to 800–1200 nm. The slight change of the nanoparticles’ shape from nanospheres of 15–30 nm to nanorods of 2.5–7.5 aspect ratio demonstrated a change in the optical properties and the resonance of gold nanoparticles to range from 500 to 1200. The definite range of 800–1200 is considered an important therapeutical range as the biological tissues are transparent to the near infra-red (NIR) light. These facts give a chance to reach good therapeutic effects in deep tissues using the photothermal and photoinaging approaches and makes the gold nanoparticles actually more precious than the pretty gold as described by Eustis and El-Sayed, 2006 [2]. Moreover, another crucial aspect is the available surface area of the obtained nanoparticles. Generally, the surface area of the nanoparticles is inversely proportional to their size. This results in a large surface area to volume ratio. Therefore, the nanoparticles possess a large surface area available for drug loading, conjugation, or binding of genes or biological moieties [3]. Accordingly, when these nanoparticles are irradiated at the appropriate wavelength, the gold nanoparticles depict an obvious absorption maximum in the visible or NIR range. If these nanoparticulate systems are well designed for the efficient targeting or internalization into the cancerous cells, then these cells can be killed eventually. Hence, the selective photo-destruction of tumours can be attained by means of laser impulses [4]. This new trend presents a new hope in the treatment of tumours and infectious diseases.

Several chemical methods and protocols are conducted to prepare the gold nanoparticles such as the chemical reduction methods. Usually in these methods, the Au\(^{3+}\) ions are reduced using mild reducing agents, such as the citrates, the tannic acid and ascorbic acid in an aqueous medium (Turkevich method). However, the main drawback of these methods is the need of the addition of organic solvents such as ethanol or acetone in order to solubilize the poorly water soluble drugs and loading these molecules on the fabricated gold nanoparticles. These organic solvents, in addition to their hazardous and unfavourable environmental effects, possess different polarity indices that highly affect the desirable nanoparticles size and their polydispersity [5]. It is worth mentioning that white phosphorus and hydrazine are agents that can also be used as reducing agents to obtain the gold nanoparticles. Nevertheless, these agents are extremely toxic.
and their resultant solutions are restricted from usage in biological applications [6].

Recently, researchers have shifted to the green methods and the use of non-toxic reagents in the gold nanoparticles preparation in order to increase the biocompatibility of the gold nanoparticles in one hand and to reduce the environmental hazards on the other. These methods include the use of plants and their constituents as safe reducing agents in the synthesis process, biological enzymatic reactions, different sugars such as the mono and poly saccharides and finally the microwave irradiation.

Plants are usually considered the nature’s chemical factory. The plants constituents and extracts will remain a treasure-trove for therapeutics [7]. Vanillic acid, caffeic acid, geraniol (cetral), menthione, linalool, gallic acid and geranyl acetate are examples of natural plant-driven reducing agents that were extracted from the leaves and fruits of *Salvia officinalis*, *Lippia citriodora*, *Pelargonium graveolens* and *Punica granatum* [8]. Furthermore, Curcumin is considered one of the most widely used plant active compounds in the preparation of gold nanoparticles [9]. The process involves the usage of plants aqueous extracts originating from the leaves, roots, flowers, seeds and barks. This extract is then centrifuged and filtered followed by the addition of HAuCl4 salt with stirring. The change in the solution colour usually indicates the formation of the colloidal gold nanoparticles. This is again followed by re-centrifugation and filtration to obtain the purified metal nanoparticles [10].

This new approach involves several advantages and some disadvantages that are summarized in Table 1.

Increasing the biocompatibility remains one of the main research milestones in the gold nanoparticles synthesis. This approach warranted the use of polymeric coatings such as polypyrrole which also imparts additional photothermal plus electro-responsive properties to the nanoparticles [1,14,15]. Advanced green method for the gold nanoparticles synthesis has also emerged; one-step synthesis of polypyrrole-coated gold nanoparticles [15]. In this method, both the polymer and gold are produced in the same step which appears as killing two birds with the same stone. Figure 1 demonstrates the redox reaction governing the one-step synthesis of these modified nanoparticles in aqueous medium.

This aforementioned method simply and successfully synthesized polypyrrole-coated gold nanoparticles (AuPpy NPs) that pose a safe alternative photothermally active multifunctional tool that is also apt for drug loading in the polypyrrole coat. This implies obtaining a triple impact weapon in combating cancer consisting of the photothermal cytotoxic effect of gold and polypyrrole in addition to the loaded chemotherapeutic agent that could be a favourable natural compound such as allicin [1,16] and curcumin [17,18].

As a future perspective, more research emphasis should be exerted on the preparation of gold nanoparticles by the green methods using the plant-driven anti-cancer polyphenolic reducing molecules such as resveratrol and sesamol as examples. The preparation of triple-function nanoparticles

| Advantages                                                                 | Disadvantages                                                                 |
|----------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Eco-friendly [11]                                                          | More insights on the mechanistic and dynamic aspects of the nanoparticles     |
| Cost-effective [12]                                                        | aspects still need to be explored [11]                                       |
| Does not include toxic reagents and chemicals [13]                        | Difficult to control the size and the shape of the nanoparticles [13]         |
|                                                                            | The feasibility of large-scale preparation of nanoparticles is still questioned [12] |

![Figure 1](image). A schematic diagram explaining the one-step synthesis method for the preparation of polypyrrole-coated gold nanoparticles (Part of the figure is drawn using Biorender.com).
such as the anticancer polyphenols-loaded polypyrrole-coated gold nanoparticles is also highly encouraged. Moreover, the use of highly compatible and naturally-driven coating or capping materials such as chitosan and gelatin [19] or exploiting them in the production of gold hybrids would allow better loading or conjugation of the anti-cancer molecules in higher amounts and would also allow the functionalization of the produced nanoparticles with ligands and targeting moieties leading to more selectivity and efficiency. These new trends appear as helping the beauty (the gold) in beating the beast (cancer).

For gold nanoparticles to appear as pharmaceutical agents in the market, a strict understanding and studying of their biodistribution/accumulation in vivo should be attained. Before performing any clinical studies, excellent characterization of the nanoparticles and good testing of the pharmacodynamics, pharmacokinetics and toxicity of the particles in a proper animal model should be conducted. This should be followed by robust statistical analyses [20]. It is worth mentioning that a number of different gold nanoparticle have successfully reached the clinical trials stages. The first of them was Aurimmune which is a thioltated PEG-coated gold nanoparticles coupled to TNF-α aiming for the targeted delivery to tumour areas. Promising results of phase I and pharmacokinetic studies were obtained. AuroShell was another example of this type of nanoparticles that reached the clinical trials. These particles are composed of thin gold layers coating a silica core. These nanoshells were proven biocompatible and well tolerated and no toxicity was reported [21].

To this end, the green synthesis of noble metal nanoparticles such as the gold nanoparticles is considered a step forward to the UN sustainable development goals (SDGs) for green chemistry including the use of less hazardous chemical syntheses, prevention of the toxic waste formation, reducing derivatives and the use of safer solvents and auxiliaries [22].

**Author contributions**

R.M.H. was responsible for conceptualization and design, analysis and interpretation of the data; the drafting of the article, revising it critically for intellectual content; and the final approval of the version to be published; and the author agrees to be accountable for all aspects of the work.

**Funding**

The author(s) reported there is no funding associated with the work featured in this article.

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