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Featured Letter

Flavonoids mediated 'Green' nanomaterials: A novel nanomedicine system to treat various diseases – Current trends and future perspective

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ABSTRACT

Nanomedicine utilizes biocompatible nanomaterials for therapeutic purposes to treat various diseases. Flavonoids present in the plant materials act as both reducing and electrostatic stabilizing agents for the 'Green' synthesis of metal nanomaterials. Further, these nanomaterials are effectively used to treat various cancer cells and pathogenic microbes. The experimental approach for flavonoids-mediated nanomaterial (FMN) synthesis is simple, rapid, cost-effective and reproducible. However, the detailed reports on synthesis, mechanism, and *in vivo* application of FMN are very limited in literatures. Thus, this focused review will definitely help researchers who are working on biocompatible nanomaterial synthesis and application in biomedical sector. Further, this is the first review to discuss the significance, mechanisms, and future trends of FMN. The FMN and their dual function as both nano-carrier and nano-drug in various biomedical sectors might be a hot research topic in upcoming days.

1. Introduction

Metal nanomaterials are known to have immense applications in the field of agriculture, energy, environment, and medicine [1]. Different kinds of physical, chemical, and biological methods have been reported for the synthesis of metal nanomaterials [2–6]. Metal nanomaterials are highly biocompatible and possess various pharmacological activities. Thus, biosynthesis and characterization of metal nanomaterials are in limelight till date [7]. Interestingly, plant based 'Green' synthesis of nanomaterials has drawn great attention due to its cost-effective, eco-friendly, non-pathogenic, rapid, and also efficiency in the treatment process. In addition, "Green" synthesis provides a single step technique as well as trouble-free to scale up for large synthesis.

2. Plant based metal nanomaterials

Since ancient times, plants have been used as natural remedies for curing many physiological disorders in traditional eastern medicine, particularly Indian and Chinese. The 'Green' synthesis of copper (Cu), gold (Au), nickel (Ni), platinum (Pt), titanium (Ti), selenium (Se), silver (Ag), and zinc nanoparticles (ZiNPs) using plant resources had been previously reported in literatures [8]. The plant based metal nanoparticles (MNPs) showed excellent antimicrobial, anticancer, antidiabetic, anti-inflammatory, antioxidant, and immunomodulatory activities [9,10]. Recently, Ahmad et al. [11], Ovais et al. [12], and Kuppusamy et al. [8] reviewed the synthesis of MNPs using different plant extract. Most of the previous reports confirm that the presence of phytochemicals such as alkaloids, flavonoids, phenols, terpenoids, alcohols, sugars, and proteins in the plant materials are involved in the reduction and stabilization of metal ions [13,14]. Although, the synthesis of MNPs using a single active substance from plant extract will be helpful for the purification of nanoparticles, and further study on such MNPs in biomedical sector is needed to treat specific diseases. At present, there is little information available in literature about a single substance from plant extract to synthesis MNPs. Recent reports highlighted the fact that flavonoids widely existing in the plant extract contributing a major role in the bioreduction of metal ionic into nanoparticle formation [5,15].

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3. Pharmacological importance of flavonoids

Flavonoids, a large class of secondary plant metabolites, are utilized for human health care due to their biological and pharmacological activities [16]. They share a common carbon skeleton of two benzene rings joined by a 3-carbon bridge (C_6-C_3-C_6), as shown in Fig. 1. The subclasses of flavonoids mentioned are anthocyanidins, flavonols, flavones, flavanones, and isoflavones [17]. Flavonoids are used to treat many pathological conditions including Alzheimer's disease, cancer, cardiovascular disorder, microbial infection, inflammatory disease, oxidative-nitrosative stress, atherosclerosis, neurodegenerative disease, and macrophage oxidation [18]. In particular, the flavonoids showed very less or no cytotoxic effect on healthy cells, while being cytotoxic against various cancer cells [19]. Apart from this, Martirosyan et al. [20] proved the protective effects of flavanoid against the cytotoxicity and oxidative stress triggered by AgNPs in normal cells. Therefore, flavonoids-mediated nanomaterial (FMN) might be a bioactive therapeutic tool to treat various diseases (Fig. 2), and also considered as an alternative to the immunosuppressive agents.

4. FMN and their biomedical efficacy

Table 1 illustrates the detail of flavonoids involved in the MNPs synthesis and their biomedical efficacy. Recently, our group found the total flavonoids present in the *Alternanthera tenella* and *Coriandrum sativum* leaf extracts majorly involved in AgNPs synthesis; and showed antiacne, antidandruff, and antibreast cancer efficacy against *Propionibacterium acnes*, *Malassezia furfur*, and human breast adenocarcinoma cells, respectively [5,15]. Zuas et al. [21] reported that the water soluble flavonoids present in *Myrmecodia pendan* extract were mainly responsible for the reduction process of Ag^+ to AgNPs. The flavonoids of *Dalbergia spinosa* leaf extract could be adsorbed onto the metal surface by interacting with carbonyl groups or electrons, and exhibited enhanced anti-inflammatory, and antibacterial (against *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*) activities [22]. Raghunandan et al. [23] noticed that flavonoids functionalized clove buds extract derived AuNPs showed anticancer activity against various cancer cells.

Aromal and Philip [24] carried out the synthesis of AuNPs using *Trigonella foenum-graecum* seed extract and concluded that flavonoids are powerful reducing agents for chloroauric acid ($HAuCl_4$) reduction. The flavonoids in the aqueous extract of *Ranunculus muricatus* interact with metal ions through coordinate covalent bond for Au/TiO_2 nanocomposite formation, and further it effectively inhibits *S. aureus* and *E. coli* [25].

Apigenin is citrus bioflavonoid, which possess antioxidant, anti-inflammatory, and anticancer activities. Kasthuri et al. [26] synthesised AuNPs and AgNPs using apiin (apigenin glycoside) extracted from *Lawsonia inermis* and expected to be an effective nano-drug to treat cancer.

Baicalein is the major bioactive flavanoid, which exhibits remarkable synergetic effects with tetracycline and *b*-lactams in the treatment of methicillin-resistant *S. aureus*. Furthermore, baicalein has been reported to attenuate the quorum sensing-controlled virulence factors including biofilm formation in *P. aeruginosa* [27]. Rajkumari et al. [28] reported the synthesis of baicalein mediated AuNPs, and confirmed their enhanced antibiofilm activity against opportunistic pathogen, *P. aeruginosa* compared to baicalein.

Dihydromyricetin (DMY) is a type of flavonol. It has multiple biological effects including hypoglycemic, antioxidant, and antibacterial activities [29,30]. Guo et al. [31] synthesised AuNPs using DMY without adding any external surfactant, capping agent or template. Furthermore, the experimental approach suggests that the flavonoid mediated AuNPs synthesis is simple, rapid, cost-effective, and reproducible.

Genistein, a naturally occurring isoflavonoid has anticancer and antiangiogenic properties [32]. Most recently, Stolarczyk et al. [33] observed that genistein reduces $Au^{3+}$to spherical Au^0

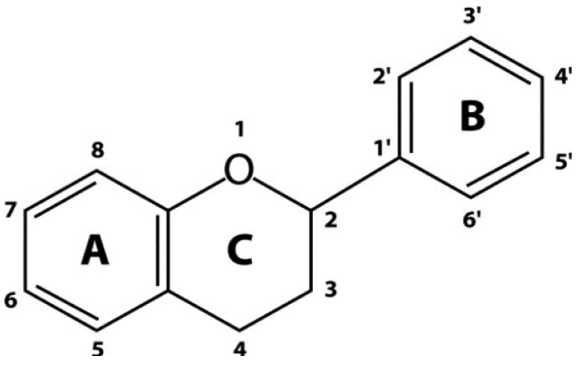

Fig. 1. Basic chemical structure of flavonoid.

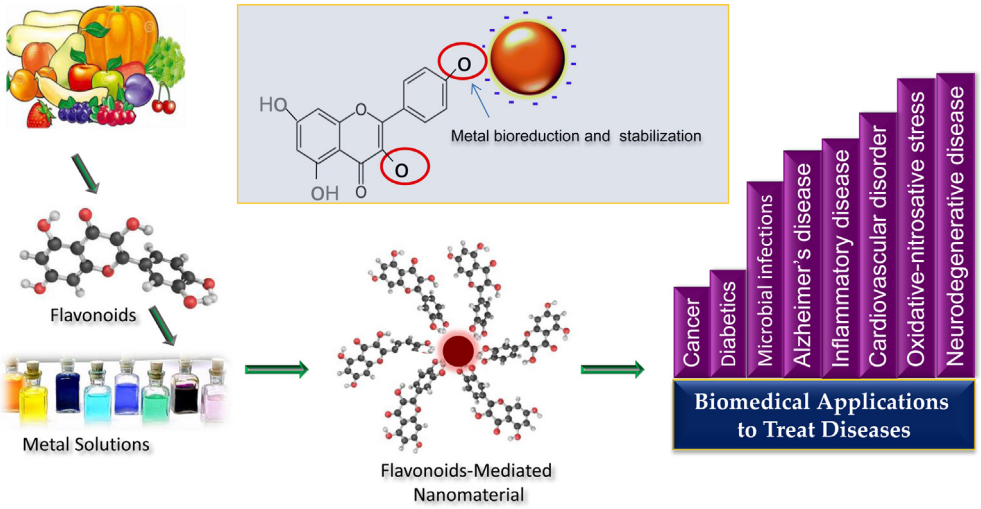

Fig. 2. Flavonoids-mediated nanomaterial (FMN) synthesis and biomedical applications.

Table 1
Mechanism and biomedical applications of FMN.

S. No.	Flavonoids	Nanomaterials	Mechanism	Biomedical applications	References
1	Apiin (Apigenin glycoside)	AuNPs (21 nm) AgNPs (39 nm)	Metal ions are reduced with the hydroxyl groups of the apiin and further oxidized to carbonyl groups. The carbonyl groups bind to metal ion and form apiin coat on nanoparticles.	Anticancer activity	[26]
2	Baicalein	AuNPs (26.5 nm)	–	Antibiofilm activity against *P. aeruginosa*	[28]
3	Catechin	c-SiNPs	–	Enhanced protective activity against oxidative stress and hippocampal cell survival	[40]
4	Dihydromyricetin	AuNPs	Hydroxyl groups involved in the reduction process	–	[31]
5	Epicatechin & Theaflavin	AgNPs (31 nm)	Carbonyl groups participated in the bioreduction of $AgNO_3$ and AgNPs stabilization.	Anticancer activity against human epidermoid larynx carcinoma cells	[41]
6	Flavonoids (*Dalbergia spinosa*)	AgNPs (18 nm)	Adsorbed onto the metal surface by interacting with carbonyl groups or electrons.	Anti-inflammatory & antibacterial (*E. coli, P. aeruginosa*, *S. aureus,* and *B. subtilis*) activities	[22]
7	Flavonoids (*Ranunculus muricatus*)	Au/TiO_2	Hydroxyl groups of flavonoids interact with metal ions through covalent bond.	Antibacterial activity against *S. aureus* and *E. coli*	[25]
8	Flavonoids (*Coriandrum sativum*)	AgNPs (37 nm)	–	Antiacne (*P. acnes*), antidandruff (*M. furfur*) & anticancer (human breast cancer) activities	[5]
9	Flavonoids (*Tephrosia tinctoria*)	AgNPs (⟨1 0 0 nm)	–	Antidiabetic activity	[42]
10	Flavonoids (*Potentilla fulgens*)	AgNPs (10–15 nm)	–	Anticancer (human breast cancer and human glioblastoma cancer cells) and antibacterial (*E. coli* and *B. subtilis*) activities.	[43]
11	Flavonoids (Andean blackberry)	AgNPs (12–50 nm)	Hydroxyl and carbonyl groups of flavonoid were adsorbed on the surface of AgNPs and involved in the reduction process.	Antioxidant activity	[46]
12	Flavonoids functionalized clove buds	AuNPs & AgNPs	–	Anticancer activities against four cancers: (i) human cervix, (ii) human chronic myelogenous, (iii) human colorectal adenocarcinoma, bone marrow and leukemia, and (iv) human kidney cancer cell.	[23]
13	Genistein	AuNPs (64.64 nm)	The electron transfer from genistein into the Au center and reduced $Au^{3+}$to Au^0. Further acted as a stabilizing agent to form a layer of negative ions converting the surface of the AuNPs.	Anticancer activities against human epithelial lung carcinoma and human melanoma cells.	[33]
14	Kaempferol	AuNPs (16.5 nm)	Hydroxyl groups in the B and C rings of kaempferol involved in the k-AuNPs formation. The A ring of k-AuNPs participated in radical scavenging activity	Anticancer activity against human breast cancer.	[34]
15	Luteolin (*Coriandrum sativum*)	AgNPs (13 nm)	Enol form of luteolin freely liberates reactive hydrogen and converts Ag^+ to Ag^0.	Antimicrobial activity against *B. subtilus*	[44]
16	Proanthocyanidin	AuNPs (17–29 nm)	–	Efficient cardio-protective potential with good biocompatibility.	[36]
17	Proanthocyanidin & Flavonol glycosides	AgNPs (20–80 nm)	–	–	[37]
18	Quercetin	Ag-SeNPs (30–35 nm)	–	Antioxidant, antimicrobial, and anticancer activities.	[39]
19	Quercetin	Metal nanoparticles	Chelate at three positions involving the carbonyl and hydroxyl groups at the C3 and C5 positions and the catechol group at the C3′ and C4′ site. These groups chelate metal ions.	–	[45]

nanocrystallites. Further, they confirmed the potentiality of having high cytotoxic activity against human melanoma cells.

Kaempferol, a flavonol is present in a variety of plant sources. Raghavan et al. [34] reported that the kaempferol participated in the formation of AuNPs, and showed promising anticancer activity against human breast cancer.

Proanthocyanidin (PAC) possesses antiviral, antiallergic, and vasodilatory activities [35]. Vinodhini et al. [36] synthesised PAC mediated AuNPs, which showed efficient cardio-protective potential with good biocompatibility. Kumar et al. [37] reported that PAC and flavonol glycosides present in the capuli cherry were mediated the AgNPs synthesis.

Quercetin can scavenge free radicals that generated by metals [38]. Mittal et al. [39] proved quercetin is mainly responsible for the reduction and stabilization of metal ions. Interestingly, the study confirmed quercetin mediated bimetallic Ag-SeNPs possess higher therapeutic efficacy in terms of antioxidant, antimicrobial, and anticancer activities.

The flavonoid catechin has been used to treat neurodegenerative diseases. Therefore, Halevas et al. [40] fabricated hybrid catechin-silica nanoparticle (c-SiNPs) and confirmed their efficient protectant effects against neuronal cell loss. Satyavani et al. [41] noticed that epicatechin and theaflavin present in the calli cells of *Citrullus colocynthis* are play a crucial role in the bioreduction of Ag^+ to AgNPs, and their stabilization.

Rajaram et al. [42] synthesised AgNPs using *Tephrosia tinctoria* and its antidiabetic activity was assessed. Further, the study confirmed enhanced bioactivity of AgNPs due to the attachment of phenol and flavonoid compounds. The flavonoid content in *Potentilla fulgens* mediated AgNPs was fourfold higher than phenolic,

indicating the role of flavonoids in the nanoparticle stabilization. This AgNPs effectively inhibited the human glioblastoma cancer cells, and also the opportunistic pathogenic microbes such as *E. coli* and *B. subtilis* [43]. However, none of the study carried out to state the efficacy of FMN for *in vivo* biomedical applications. Thus, further studies needed to compare the pharmacological efficacy of individual flavanoid and its mediated MNPs to know their accurate biomedical functions.

5. Mechanism of nanomaterial formation by flavonoids

Few studies have proposed the possible mechanism for flavonoids interaction with metal ions to nanomaterial formation (Table 1). According to Raghavan et al. [34], the hydroxyl groups present in the B and C rings of kaempferol may participate in the AuNPs formation. Further, the A ring of kaempferol coated on the surface of AuNPs may be responsible for the radical scavenging activity. Nazeruddin et al. [44] reported the formation of enol form of the luteolin which freely liberates reactive hydrogen, is responsible for the conversion of Ag^{+} to Ag^{0}.

Guo et al. [31] reported the formation of AuNPs by DMY through the oxidation of hydroxyl to carbonyl groups. The study found that the stretching vibration of DMY hydroxy groups shifted to higher wavenumber after bioreduction, which indicated that hydroxy groups participated in the reaction. In addition, the stretching vibration of carbonyl groups shifted to lower wavenumber due to the oxidation of hydroxyl groups and the formation of intramolecular hydrogen bonds.

Quercetin can chelate at three positions involving the carbonyl and hydroxyl groups at the C3 and C5 positions and the catechol group at the C3′ and C4′ site. These groups chelate different metal ions by the following steps: (i) adsorbed onto the metal surface, (ii) budding of nanoparticle, (iii) aggregation, and (iv) bioreduction [45]. Stolarczyk et al. [33] proposed the mechanism for genistein-AuNPs complex formation as follows: (i) the electron transfer from genistein into the Au center, (ii) the genistein reduced Au^{3+} to Au^{0}, and (iii) further acted as a stabilizing agent to form a layer of negative ions converting the surface of the AuNPs.

Kumar et al. [46] observed the hydroxyl and carbonyl groups of flavonoids present in the Andean blackberry fruit extract were adsorbed on the surface of AgNPs and involved in the reduction process. Kasthuri et al. [26] revealed that Au^{3+}/Ag^{+}ions were reduced by hydroxyl groups of the apiin, and the hydroxyl groups were further oxidized to carbonyl groups. Then, the carbonyl groups of apiin bind to metal ion and form over coating on the nanoparticles to prevent gathering. Most of these available literatures clearly suggest that both hydroxyl and carbonyl groups present in the flavonoids are collectively playing a major role in the formation of FMN (Fig. 2). To conclude, the efficiency of nanomaterial formation by flavonoids depends on the number of hydroxyl group and carbonyl group in the 'A', 'C', and 'B' rings of the flavonoid structure. The chemical modification of hydroxyl and carbonyl groups may provide insight into the importance of number and positioning of these groups in the formation of nanomaterials.

6. Dual function of FMN to treat various diseases

As mentioned above, flavonoids find a wide range of applications. However, flavonoids impede their bioactivity *in vivo* applications, due to their low absorption, poor stability, insolubility, passive diffusion, and active efflux in the gastrointestinal (GI) tract [47]. Interestingly, novel drug delivery system using nanomaterials with a broad spectrum of applications offer a new therapeutic base for scientific integration and innovation. Recent literatures proved that metal based nanomaterials are acting as both nano-carrier and nano-drug for various routes of administration as well as rapid recognition by the immune system [28,33]. In these flavonoids-nanoparticles complex, nanoparticles interact with flavonoids via hydrogen bonds and hydrophobic interactions which can enhance aqueous solubility of flavonoids at target sites. Importantly, nanoparticles may protect flavonoids against decomposition process occurring in the GI, and further nanoparticles can be taken directly up by epithelial cells in small intestine, which significantly increases absorption and bioavailability of flavonoids [48].

Nanoparticles are established with hydrophobic groups inside and polar groups on surface of particles. For example, Zou et al. [49] achieved encapsulation of procyanidin into zein nanoparticles and observed increased procyanidin solubility in aqueous system. MNPs synthesised by different methods have been used as a nano-carrier for flavanoid delivery. Hsieh et al. [50] studied the physical attachment of epigallocatechin-3-gallate onto the surface of AuNPs, and confirmed the more effective inhibition of bladder cancer in model mice. Thus, this review proposes FMN might work as biocompatible nano-carrier for flavonoid delivery as well as nano-drug to treat specific targeted diseases in single system.

7. Conclusions and future perspective

Recently, there is a surge and focus of activity on preparation and characterization of flavonoids based nanomaterials in various capacities using the 'Green' synthesis. Detailed research is warranted on mechanistic evaluation of the flavonoid-metal-complexes in solution and *in vivo*. Modern research is now focused on developing single molecule based nano-conjugates and some of these formulations have promising potential in nanomedicine. Overall it appears that even though there has been significant progress, a great deal can still be expected with the developments in the field of nanoscience which may focus on single molecule based nanomaterials such as bimetallic alloy nanoparticles which might be more advantageous over ordinary MNPs. FMN to move into the clinical arena, it is important that a systematic approach to test the safety of nanoparticles, including the sub-lethal cellular changes, should be foremostly established. Future work would be focused on FMN designed for oral administration, superior gastrointestinal stability, mucus penetrating function, and intestinal epithelial cell targeting properties.

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References

[1] S.P. Chandran, M. Chaudhary, R. Pasricha, A. Ahmad, M. Sastry, Synthesis of gold nanotriangles and silver nanoparticles using *Aloe vera* plant extract, Biotechnol. Prog. 22 (2006) 577–583.
[2] J.M. Allen, J. Xu, M. Blahove, S.A. Canonico-May, T.J. Santaloci, M.E. Braselton, M. Blahove, J.W. Stone, Synthesis of less toxic gold nanorods by using dodecylethyldimethylammonium bromide as an alternative growth-directing surfactant, J. Colloid Interf. Sci. 505 (2017) 1172–1176.
[3] L. Biao, S. Tan, Y. Wang, X. Guo, Y. Fu, F. Xu, Y. Zu, Z. Liu, Synthesis, characterization and antibacterial study on the chitosan-functionalized Ag nanoparticles, Mater. Sci. Eng. C 76 (2017) 73–80.
[4] M. Karimi, M.R. Ramsheh, S.M. Ahmadi, M.R. Madani, M. Shamsi, R. Reshadi, F. Lotfi, Reline-assisted green and facile synthesis of fluorapatite nanoparticles, Mater. Sci. Eng. C 77 (2017) 121–128.

[5] P. Sathishkumar, J. Preethi, R. Vijayan, A.R. Mohd Yusoff, F. Ameen, S. Suresh, R. Balagurunathan, T. Palvannan, Anti-acne, anti-dandruff and anti-breast cancer efficacy of green synthesised silver nanoparticles using *Coriandrum sativum* leaf extract, J. Photochem. Photobiol. B 163 (2016) 69–76.
[6] X. Ye, L. Chen, L. Liu, Y. Bai, Electrochemical synthesis of selenium nanoparticles and formation of sea urchin-like selenium nanoparticles by electrostatic assembly, Mater. Lett. 196 (2017) 381–384.
[7] C.K. Venil, P. Sathishkumar, M. Malathi, R. Usha, R. Jayakumar, A.R. Mohd Yusoff, W. Azlina Ahmad, Synthesis of flexirubin-mediated silver nanoparticles using *Chryseobacterium artocarpi* CECT 8497 and investigation of its anticancer activity, Mater. Sci. Eng. C 59 (2016) 228–234.
[8] P. Kuppusamy, M.M. Yusoff, G.P. Maniam, N. Govindan, Biosynthesis of metallic nanoparticles using plant derivatives and their new avenues in pharmacological applications - an updated report, Saudi Pharm. J. 24 (2016) 473–484.
[9] D. Rehana, D. Mahendiran, R. Senthil, Kumar, A. Kalilur Rahiman, In vitro antioxidant and antidiabetic activities of zinc oxide nanoparticles synthesized using different plant extracts, Bioprocess. Biosyst. Eng. 40 (2017) 943–957.
[10] N.J. Reddy, D.N. Vali, M. Rani, S.S. Rani, Evaluation of antioxidant, antibacterial and cytotoxic effects of green synthesized silver nanoparticles by *Piper longum* fruit, Mater. Sci. Eng. C 34 (2014) 115–122.
[11] B. Ahmad, N. Hafeez, S. Bashir, A. Rauf, M. Rehman, Phytofabricated gold nanoparticles and their biomedical applications, Biomed. Pharmacother. 89 (2017) 414–425.
[12] M. Ovais, A. Raza, S. Naz, N.U. Islam, A.T. Khalil, S. Ali, M.A. Khan, Z.K. Shinwari, Current state and prospects of the phytosynthesized colloidal gold nanoparticles and their applications in cancer theranostics, Appl. Microbiol. Biotechnol. 101 (2017) 3551–3565.
[13] N. Jayaprakash, J.J. Vijaya, K. Kaviyarasu, K. Kombaiah, L.J. Kennedy, R.J. Ramalingam, M.A. Munusamy, H.A. Al-Lohedan, Green synthesis of Ag nanoparticles using Tamarind fruit extract for the antibacterial studies, J. Photochem. Photobiol. B 169 (2017) 178–185.
[14] B. Khodadadi, M. Bordbar, M. Nasrollahzadeh, Green synthesis of Pd nanoparticles at Apricot kernel shell substrate using Salvia hydrangea extract: Catalytic activity for reduction of organic dyes, J. Colloid Interf. Sci. 490 (2017) 1–10.
[15] P. Sathishkumar, K. Vennila, R. Jayakumar, A.R. Mohd Yusoff, T. Hadibarata, T. Palvannan, Phyto-synthesis of silver nanoparticles using *Alternanthera tenella* leaf extract: an effective inhibitor for the migration of human breast adenocarcinoma (MCF-7) cells, Bioprocess Biosyst. Eng. 39 (2016) 651–659.
[16] G. Dehghan, Z. Khoshkam, Tin (II)-quercetin complex: synthesis, spectral characterisation and antioxidant activity, Food Chem. 131 (2012) 422–426.
[17] S. Wang, J. Zhang, M. Chen, Y. Wang, Delivering flavonoids into solid tumors using nanotechnologies, Expert Opin. Drug Deliv. 10 (2013) 1–18.
[18] N. Koirala, N.H. Thuan, G.P. Ghimire, D.V. Thang, J.K. Sohng, Methylation of flavonoids: chemical structures, bioactivities, progress and perspectives for biotechnological production, Enzyme Microb. Tech. 86 (2016) 103–116.
[19] M. Sghaier, I. Skandrani, N. Nasr, M.G. Franca, L. Chekir-Ghedira, K. Ghedira, Flavonoids and sesquiterpenes from *Tecurium ramosissimum* promote antiproliferation of human cancer cells and enhance antioxidant activity: a structure-activity relationship study, Environ. Toxicol. Pharmacol. 32 (2011) 336–348.
[20] A. Martirosyan, K. Grintzalis, M. Polet, L. Laloux, Y.J. Schneider, Tuning the inflammatory response to silver nanoparticles via quercetin in Caco-2 (co-)cultures as model of the human intestinal mucosa, Toxicol. Lett. 253 (2016) 36–45.
[21] O. Zuas, N. Hamim, Y. Sampora, Bio-synthesis of silver nanoparticles using water extract of *Myrmecodia pendan* (Sarang Semut plant), Mater. Lett. 123 (2014) 156–159.
[22] N. Muniyappan, N.S. Nagarajan, Green synthesis of silver nanoparticles with *Dalbergia spinosa* leaves and their applications in biological and catalytic activities, Process Biochem. 49 (2014) 1054–1061.
[23] D. Raghunandan, B. Ravishankar, G. Sharanbasava, D.B. Mahesh, V. Harsoor, M. S. Yalagatti, M. Bhagawanraju, A. Venkataraman, Anti-cancer studies of noble metal nanoparticles synthesized using different plant extracts, Cancer Nanotechnol. 2 (2011) 57–65.
[24] S.A. Aromal, D. Philip, Green synthesis of gold nanoparticles using *Trigonella foenum-graecum* and its size-dependent catalytic activity, Spectrochim. Acta A Mol. Biomol. Spectrosc. 97 (2012) 1–5.
[25] K. Tahir, A. Ahmad, B. Li, A.U. Khan, S. Nazir, S. Khan, Z.U.H Khan, S.U. Khan, Preparation, characterization and an efficient photocatalytic activity of Au/TiO_2 nanocomposite prepared by green deposition method, Mater. Lett. 178 (2016) 56–59.
[26] J. Kasthuri, S. Veerapandian, N. Rajendiran, Biological synthesis of silver and gold nanoparticles using apiin as reducing agent, Colloid. Surface. B 68 (2009) 55–60.
[27] J. Luo, J. Kong, B.Y. Dong, H. Huang, K. Wang, L.H. Wu, Y.Q. Chen, Baicalein attenuates the quorum sensing-controlled virulence factors of *Pseudomonas aeruginosa* and relieves the inflammatory response in *P. aeruginosa*-infected macrophages by down regulating the MAPK and NFkB signal-transduction pathways, Drug. Des. Devel. Ther. 10 (2016) 183–203.
[28] J. Rajkumari, S. Busi, A.C. Vasu, P. Reddy, Facile green synthesis of baicalein fabricated gold nanoparticles and their antibiofilm activity against *Pseudomonas aeruginosa* PAO1, Microb. Pathog. 107 (2017) 261–269.
[29] J.H. Gao, B.G. Liu, Z.X. Ning, R.X. Zhao, A.Y. Zhang, Q. Wu, Characterization and antioxidant activity of flavonold-rich extracts from leaves of *Ampelopsis grossedentata*, J. Food Biochem. 33 (2009) 808–820.
[30] G. Cao, E. Sofic, R.L. Prior, Antioxidant and prooxidant behavior of flavonoids: structure-activity relationships, Free Rad. Biol. Med. 22 (1997) 749–760.
[31] Q. Guo, Q. Guo, J. Yuan, J. Zeng, Biosynthesis of gold nanoparticles using a kind of flavonol: Dihydromyricetin, Colloids Surf. A 441 (2014) 127–132.
[32] C.Z. Radzikowski, J. Wietrzyk, G. Grynkiewicz, A. Opolski, Genisteina - izoflawonoid soi o zróżnicowanym mechanizmie działania-implikacje kliniczne w lecznictwie i prewencji chorób nowotworowych, Postępy Hig. Med. Dośw. 58 (2004) 128–139.
[33] E.U. Stolarczyk, K. Stolarczyk, M. Laszcz, M. Kubiszewski, W. Maruszak, W. Olejarz, D. Bryk, Synthesis and characterization of genistein conjugated with gold nanoparticles and the study of their cytotoxic properties, Eur. J. Pharm. Sci. 1 (2017) 176–185.
[34] B.S. Raghavan, S. Kondath, R. Anantanarayanan, R. Rajaram, Kaempferol mediated synthesis of gold nanoparticles and their cytotoxic effects on MCF-7 cancer cell line, Process Biochem. 50 (2015) 1966–1976.
[35] D. Bagchi, M. Bagchi, S.J. Stohs, D.K. Das, S.D. Ray, C.A. Kuszynski, S.S. Joshi, H.G. Pruess, Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention, Toxicology 148 (2000) 187.
[36] A. Vinodhini, K. Govindaraju, G. Singaravelu, A. Mohamed Sadiq, V. Ganesh Kumar, Cardioprotective potential of biobased gold nanoparticles, Colloid. Surface. B 1 (2014) 480–486.
[37] B. Kumar, Y. Angulo, K. Smita, L. Cumbal, A. Debut, Capuli cherry-mediated green synthesis of silver nanoparticles under white solar and blue LED light, Particuology 24 (2016) 123–128.
[38] A.F. Santos, D.F. Brotto, L.R. Favarin, N.A. Cabeza, G.R. Andrade, M. Batistote, A. A. Cavalheiro, A. Neves, D. Rodrigues, A.D. Anjos, Study of the antimicrobial activity of metal complexes and their ligands through bioassays applied to plant extracts, Rev. Bras. Farmacogn. 24 (2014) 309–315.
[39] A.K. Mittal, S. Kumar, U.C. Banerjee, Quercetin and gallic acid mediated synthesis of bimetallic (silver and selenium) nanoparticles and their antitumor and antimicrobial potential, J. Colloid Interf. Sci. 431 (2014) 194–199.
[40] E. Halevas, C.M. Nday, A. Salifoglou, Hybrid catechin silica nanoparticle influence on Cu(II) toxicity and morphological lesions in primary neuronal cells, J. Inorg. Biochem. 163 (2016) 240–249.
[41] K. Satyavani, S. Gurudeeban, T. Ramanathan, T. Balasubramanian, Biomedical potential of silver nanoparticles synthesized from calli cells of *Citrullus colocynthis* (L.) Schrad, J. Nanobiotechnol. 9 (2011) 43–50.
[42] K. Rajaram, D.C. Aiswary, P. Sureshkumar, Green synthesis of silver nanoparticle using *Tephrosia tinctoria* and its antidiabetic activity, Mater. Lett. 138 (2015) 251–254.
[43] A.K. Mittal, D. Tripathy, A. Choudhary, P.K. Aili, A. Chatterjee, I.P. Singh, U.C. Banerjee, Bio-synthesis of silver nanoparticles using *Potentilla fulgens* Wall. exHook. and its therapeutic evaluation as anticancer and antimicrobial agent, Mater. Sci. Eng. C 53 (2015) 120–127.
[44] G.M. Nazeruddin, N.R. Prasad, S.R. Prasad, Y.I. Shaikh, S.R. Waghmare, P. Adhyapak, *Coriandrum sativum* seed extract assisted in situ green synthesis of silver nanoparticle and its anti-microbial activity, Ind. Crops Prod. 60 (2014) 212–216.
[45] V.V. Makarov, A.J. Love, O.V. Sinitsyna, S.S. Makarova, I.V. Yaminsky, M.E. Taliansky, N.O. Kalinina, "Green" nanotechnologies: synthesis of metal nanoparticles using plants, Acta Nat. 6 (2014) 35–44.
[46] B. Kumar, K. Smita, L. Cumbal, A. Debut, Green synthesis of silver nanoparticles using Andean blackberry fruit extract, Saudi J. Biol. Sci. 24 (2017) 45–50.
[47] J. Liang, H. Yan, P. Puligundla, X. Gao, Y. Zhou, X. Wan, Applications of chitosan nanoparticles to enhance absorption and bioavailability of tea polyphenols: a review, Food Hydrocolloid. 69 (2017) 286–292.
[48] Z. Li, H. Jiang, C. Xu, L. Gu, A review: Using nanoparticles to enhance absorption and bioavailability of phenolic phytochemicals, Food Hydrocolloid. 43 (2015) 153–164.
[49] T. Zou, Z. Li, S.S. Percival, S. Bonard, L. Gu, Fabrication, characterization, and cytotoxicity evaluation of cranberry procyanidins-zein nanoparticles, Food Hydrocolloid. 27 (2012) 293–300.
[50] D.S. Hsieh, H. Wang, S.W. Tan, Y.H. Huang, C.Y. Tsai, M.K. Yeh, C.J. Wu, The treatment of bladder cancer in a mouse model by epigallocatechin-3-gallate-gold nanoparticles, Biomaterials 32 (2011) 7633–7640.