

Review Article

UMBELLIFERONE-LOADED SELENIUM NANOPARTICLES: A PROMISING NANOPLATFORM FOR ENHANCED THERAPEUTIC DELIVERY

Kuldeep Kumar¹, Shabana Kausar Khan¹, Jagdish Chandra Nagar¹ and Mukesh Mehra^{*2}

¹Kota College of Pharmacy, Kota-324003-Rajasthan, India

²Lord Buddha College of Pharmacy, Kota-324005-Rajasthan, India

Email: mehrasang@gmail.com

ABSTRACT

Umbelliferone, 7-hydroxycoumarin, is a natural 7 OH coumarin that is widely found in medicinal plants of the Apiaceae and Rutaceae families. It has garnered a lot of interest due to its antioxidant, anti-inflammatory, antimicrobial, antihyperglycaemic and anticancer properties. However, many bioactive molecules derived from plants have therapeutic potential, yet are limited by various physicochemical and biopharmaceutical properties including low water solubility, bioavailability and low half-life in biological systems. Nanotechnology is a way to provide solutions to some of these problems. Among the different nanomaterials investigated for biomedical applications, selenium nanoparticles (SeNPs) are particularly interesting because selenium is an essential trace element and nanoscale selenium has been explored for antioxidant, antimicrobial and anticancer applications. It has been recently shown that SeNPs can be used in combination with natural compounds containing coumarin. In a 2026 study, umbelliprenin showed more effect on the viability of MDA-MB-231 breast cancer cells and decreased expression of MMP-2, MMP-9 and ICAM-1 when compared with the individual components. This finding is structurally different from umbelliferone; however, it offers a rationale to exploring similar coumarin-SeNP systems. More directly, in a 2026 report, spherical SeNPs in the reported 50–150 nm range were reported as being synthesized with umbelliferone, and the authors showed that there was an interaction between the two and a prolonged release of umbelliferone. This short review summarizes the pharmacological potential of umbelliferone, the rationale for selenium nanoparticle-based delivery, reported approaches for preparation and characterization of UMB-SeNPs, their possible therapeutic advantages, and the research questions that remain before this system can progress toward in vivo and clinical evaluation.

KEY WORDS

Umbelliferone; selenium nanoparticles; nanocarriers; coumarin; green synthesis; drug delivery; controlled release; nanomedicine

1. INTRODUCTION

Natural products continue to provide an important source of pharmacologically active molecules. Of these, coumarins have been much studied as they have been shown to have a wide spectrum of biological activity with small structural modifications in the coumarin structure. One such natural coumarin is “umbelliferone” (7-hydroxycoumarin or β -

umbelliferone). It is present in several plant species and it is mainly present in the family Apiaceae and Rutaceae and has been studied for its anti-oxidant, anti-inflammatory, anti-microbial, anti-hyperglycaemic and anticancer properties. [1] Although this wide pharmacological spectrum, the transformation of umbelliferone into an effective pharmaceutical formulation is not simple.

The solubility, stability, absorption or drug exposure at the intended site of action may not be adequate when using conventional delivery methods. Thus, various nanocarrier systems have been developed for umbelliferone such as solid lipid nanoparticles, phytosomes, polymeric nanoparticles, micelles and mesoporous silica nanoparticles. [1] Singh and Rahman have recently reviewed the current development of nanocarriers of umbelliferone and the ability to alter properties like solubility, stability and drug release and bioavailability via nanosystems in the year 2020. [2]. Several methods to include umbelliferone in nanoscale delivery systems were mentioned in the same review, indicating that nanotechnology could offer a beneficial pathway for enhancing the pharmaceutical attributes of umbelliferone. Another interesting platform are selenium nanoparticles. In contrast to numerous metallic nanoparticles, selenium is a micronutrient that is necessary for human health, and nanoselenium has been studied for its biological activity and relatively low toxicity. Besides acting as a nanocarrier, SeNPs can also exert their own pharmacological activities. The recent discovery of SeNPs loaded with umbelliferone thus provides an interesting example of the marriage of natural-product pharmacology and nanomedicine. The idea is especially appealing as the nanoparticle could be used to enhance the delivery and selenium could add biological activity. [3]

2.UMBELLIFERONE: PHARMACOLOGICAL POTENTIAL AND FORMULATION CHALLENGES

Umbelliferone is a basic coumarin which has a hydroxyl group at position 7. The structure is responsible for its antioxidant and other biological properties. A brief summary of the previous studies reported in the literature indicated antibacterial, antifungal, antioxidant, anti-inflammatory, antihyperglycaemic, antidiabetic, anticancer, analgesic and hepatoprotective activities [1]. The compound also has been studied as a lead compound for further drug delivery development. But successful therapeutic use is not assured by biological activity alone. The ultimate pharmacological activity may be affected by a number of factors including absorption, solubility, stability, and tissue distribution and intracellular availability. In this respect, nanocarriers are useful since the properties of the drug containing system can be changed by reducing its size to the nano-scale, such as its surface area, dispersibility, interaction with biological membranes, and release behavior. Nanoparticles can also act as a buffer to help prevent the premature degradation of an active molecule and offer more controlled delivery, depending on the carrier. [4] There are a number of examples of this method. The umbelliferone has been previously used in solid lipid nanoparticles, phytosomal systems and polymeric or silica nanosystems. A study that was particularly relevant was the creation of folic-acid-functionalized, pH responsive mesoporous silica nanoparticles containing umbelliferone. It was designed to be tumour targeted and exhibited increased anticancer activity compared to free umbelliferone in the experimental model investigated. [2] The

results are important to take into account for the consideration of selenium as an alternative nanoparticle platform.

3. WHY SELENIUM NANOPARTICLES?

Selenium is of double significance for nanomedicine. Selenium is an essential trace element, with a variety of biological functions, primarily related to antioxidant defence. Second, selenium has physicochemical properties that are different from its bulk form and selenium salts at the nanoscale. SeNPs have been investigated as carriers as well as biologically active nanoparticles. [5] Advantages that they offer is that they are very small, have a very high surface area, and can be modified on the surface. Their biological activities have been linked to the regulation of oxidative stress, cell signaling and regulation of cell survival and proliferation in cancer models. In the study uploaded in 2026, the study of umbelliprenin-SeNPs is a good example of this concept. In this study, biogenic SeNPs were synthesized with the use of *Lactobacillus plantarum*. [6] The particles were mostly spherical in shape, having a hydrodynamic diameter of ~135-150 nm and a negative zeta potential of ~-30 mV. The researchers also found that the treatment with the coumarin derivative, umbelliprenin, along with SeNPs was more cytotoxic when compared to either treatment alone in the MDA-MB-231, a triple-negative breast cancer cell line. This mixture also decreased the expression of MMP-2, MMP-9 and ICAM-1 and blocked cell migration. [3] It is important to note that the results of these studies cannot be used to conclude that umbelliferone-SeNPs

have the same effects. Umbelliprenin and umbelliferone are two different molecules. Instead, the study shows the potential of the general application of bioactive coumarin compound with selenium nanoparticles.

4. UMBELLIFERONE-LOADED SELENIUM NANOPARTICLES

Tiwari and Thagele reported in 2026 the direct development of UMB-SeNPs. In this study, the green synthesis method was described in which the selenium nanoparticles were formed using umbelliferone. The reported formulation resulted in the formation of mostly spherical particles of the range 50–150 nm. UV-visible spectroscopy, SEM, TEM, EDX, XRD and FTIR were used for characterization. The study provided spectroscopic and microscopic evidence for the formation of nanoparticles and interaction of the surface of the selenium nanoparticle with umbelliferone. In vitro release experiments also showed sustained and controlled release as compared to the free umbelliferone. [4] From a formulation point of view, this is of particular interest as the active compound is also part of the formulation. The green synthesis process may also help to decrease the use of harsh chemical reducing agents, and it could be a more straightforward method for the synthesis of biologically compatible nanoparticles. The reported results are mainly physicochemical and in vitro however. Further studies are required to ascertain if the enhanced release and stability lead to enhanced pharmacokinetics, tissue distribution and therapeutic efficacy in living systems.[6]

5. POSSIBLE MECHANISM OF THERAPEUTIC ACTION

There are two complementary approaches to consider the therapeutic potential of UMB-SeNPs: biological activity of umbelliferone and intrinsic properties of selenium nanoparticles. Umbelliferone has been reported to affect a number of cell pathways and to possess antioxidant and anti-inflammatory properties. The previous literature review highlighted its anti-inflammatory, anti-oxidative and possible anticancer properties. [1] Other biological effects may be achieved with selenium nanoparticles. In the 2026 umbelliprenin-SeNP study, activation of the p53 pathway, and inhibition of the PI3K/Akt and NF- κ B pathway were proposed as being involved in the biological activity of SeNPs.[3]

A simplified proposed mechanism for UMB-SeNPs can therefore be represented as [7]:

UMB-SeNP administration → improved nanoparticle-mediated cellular interaction → enhanced umbelliferone availability → modulation of oxidative and inflammatory signaling → altered cell survival/proliferation pathways → potential antioxidant, anti-inflammatory and anticancer effects

This should currently be regarded as a **working mechanistic framework**, rather than a fully established mechanism for UMB-SeNPs. Direct mechanistic studies using the UMB-SeNP formulation are still required.

6. CHARACTERIZATION OF UMB-SENPS

A complete characterization strategy is essential before considering biological evaluation. The following parameters are particularly relevant.

6.1 Size and shape of particles:

The size of the particle influences its uptake by cells, distribution and physical stability. SEM and TEM can give information about the morphology of a particle and the primary particle size, while DLS will give information about the hydrodynamic diameter in dispersion. In the direct UMB-SeNP study, it was reported that most of the particles were spherical and in the size range 50–150 nm [4]. The hydrodynamic size of the SeNPs used in the 2026 umbelliprenin study was around 135–150 nm [3] compared to the ca. 70–100 nm size of the biogenic SeNPs. [8]

6.2 Surface charge:

Zeta potential gives information about the surface charge and the stability of the colloids. Electrostatic repulsion can be used to minimize particle aggregation when the surface is sufficiently charged. The zeta potential value for umbelliprenin-SeNP was found to be centered around –30 mV, which is a value indicative of good colloidal stability. [9]

6.3 Chemical interaction:

FTIR can provide information on the changes in the characteristic functional groups of the materials, as well as possible interaction between umbelliferone and the surface of the nanoparticle. XRD can offer data on the crystalline properties and EDX can verify the element composition of selenium-containing particles. [10]

6.4 Drug loading and release:

The amount of drugs loaded and encapsulated or associated should be determined by a validated analytical method. In vitro release studies are also crucial because the key formulation benefit should not just be in terms of the formation of nanoparticles, but in terms of improved and controlled release. Sustained release was mentioned in the published UMB-SeNP report in comparison to free umbelliferone. [11]

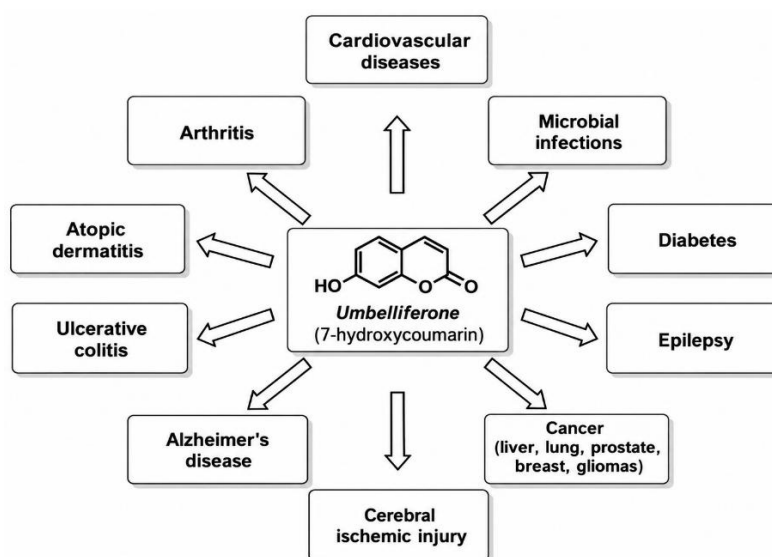
7.POTENTIAL BIOMEDICAL APPLICATIONS

The biological profile of umbelliferone suggests several possible applications for UMB-SeNPs. Anticancer applications one of the most fascinating regions for study at this time. Umbelliferone has been used in the past as an anticancer agent and selenium nanoparticles have also been shown to have anticancer activity in experimental models. In a study on coumarin-SeNP using umbelliprenin, viability and migration of the MDA-MB-231 cells was reduced, and the expression of MMP-2, MMP-9 and ICAM-1 was

downregulated. [12] Umbelliferone was also successfully loaded into targeted mesoporous silica nanoparticles that were shown to improve anticancer effects and to induce oxidative stress and mitochondrial damage in the examined breast cancer model. [13]. These results together offer a good pretext to consider the use of UMB-SeNPs in cancer models, but it is necessary to have further evidence.

Umbelliferone is known to possess antioxidant and anti-inflammatory properties. The nanocarrier strategy may enhance its stability and bioavailabilities. Sustained release and good physicochemical properties were specifically mentioned in the 2026 UMB-SeNP report, but not clinical antioxidant or anti-inflammatory activity [14].

Other possible applications Previously, umbelliferone loaded nanocarriers were investigated for their antimicrobial, metabolic, dermatological and biomedical applications. [15] These applications should be considered as possible future areas of research, however, and are not approved treatments for UMB-SeNPs.



8. ADVANTAGES AND LIMITATIONS

The UMB-SeNPs are unique because they combine two biologically active ingredients. Umbelliferone provides the pharmacological activity of a natural coumarin, and the selenium nanoparticles could also serve as a delivery system as well as being a biologically active ingredient. Potential advantages include [16,17]:

- Nanoscale Particle Size and Large Surface Area;
- Enhanced Bioavailability of Umbelliferone;
- Controlled Release; • Enhanced Cell Attachment;
- High Purity;
- Pharmacological Activity of The Combination of Umbelliferone and Selenium; and
- Opportunities For Surface Modification and Targeted Delivery.

Meanwhile, there are some questions which have not been answered. Synthesis conditions can result in significantly different sizes and surface properties of the nanoparticles. Another consideration for selenium dose is that the biological activity and toxicity may be related to particle size, surface chemistry, and concentration. Long-term stability, protein corona formation, pharmacokinetics (PK), biodistribution and elimination should be carefully evaluated. Most significant is the continued prevalence of physicochemical characterization and in vitro studies. The conclusions of the study itself in 2026 [3] were that additional animal and clinical studies are needed.

9. FUTURE PERSPECTIVES

Future studies of UMB-SeNPs should include the demonstration of the formation of nanoparticles beyond. A systematic formulation-development strategy is needed. Optimising the synthesis conditions with regard to particle size, polydispersity, surface charge, selenium content and loading of umbelliferone is required first. Secondly, the formulation should be tested for accelerated and long-term stability. Third, the release kinetics should be investigated under physiologically relevant conditions. The next step in biological evaluation would then be to use suitable animal models. Specific pharmacokinetic studies to compare free umbelliferone and UMB-SeNPs would be of special value. Tissue Distribution studies may help determine if exposure at the desired site is increased with the formulation of the nanoparticles. In the context of anticancer applications, other studies should also focus on the effects of cytotoxicity, apoptosis, cell cycle, oxidative stress, mitochondrial function, migration and invasion. Studies on the pathways involving NF- κ B, PI3K/Akt and p53 may be helpful in elucidating the mechanism by which they are set in motion, whether it be umbelliferone, selenium, or both. Last, but not least, toxicity studies in normal cells and animals are needed. The therapeutic benefit of the use of a nanoparticle formulation cannot be assumed just because it is more cytotoxic in the cancer cell. [18-20]

10. CONCLUSION

Emerging approach is the combination of the pharmacological potential of a natural coumarin, umbelliferone, with the

physicochemical and biological properties of nanoselenium, which is loaded with umbelliferone. Earlier published studies have demonstrated that the umbelliferone can be engineered into various nanocarrier systems and recent studies have confirmed the preparation of nanoscale size UMB-SeNPs, successful interaction between selenium and umbelliferone and sustained release. It is important to note that the recent study on umbelliprenin-SeNPs further supports the study of coumarin-selenium combinations, especially in cancer models; however, the results should not be directly correlated to the coumarin component, umbelliferone. In summary, currently UMB-SeNPs appear to be a useful research tool but not a therapeutic system. The actual benefit of these physicochemical changes observed in vitro will rely on their in vivo functionality and efficacy as well as safety profiles.

REFERENCES

1. Singh D, Rahman M. Umbelliferone loaded nanocarriers for healthcare applications. *Curr Biochem Eng.* 2020;6(1):25–33. doi:10.2174/2212711906666190730100144.
2. Tumor targeted delivery of umbelliferone via a smart mesoporous silica nanoparticles controlled-release drug delivery system for increased anticancer efficiency. *Mater Sci Eng C Mater Biol Appl.* 2020;117:111239. doi:10.1016/j.msec.2020.111239.
3. Azimi F, Shahverdi AR, Shamsnia HS, Yazdi MH. Umbelliprenin co-formulated with selenium nanoparticles downregulates MMP-2, MMP-9 and ICAM-1 expression in triple-negative breast cancer cells MDA-MB-231. *BMC Complement Med Ther.* 2026. doi:10.1186/s12906-026-05445-9.
4. Tiwari B, Thagele R. Green synthesis and characterization of umbelliferone-loaded selenium nanoparticles. *Int J Drug Deliv Technol.* 2026;16(51s). doi:10.25258/ijddt.16.51s.157.
5. Mahmoodi Khatonabadi S, Salami S, Mirfakhraie R, Atabakhshian R, Sirati-Sabet M, Yaghmaei BG, et al. Umbelliprenin Inhibited Angiogenesis and Metastasis of MDA-MB-231 Cell Line through Downregulation of CoCl₂/EGF Mediated PI3K/AKT/ERK Signaling. *Middle East Journal of Cancer.* 2022;13(2):226–36.
6. Dose-dependent efficacy of umbelliferone and gelatin-coated ZnO/ZnS core-shell nanoparticles: a novel arthritis agent for severe knee arthritis. *Biomed Res Int.* 2022;2022:7795602.
7. Boik J. Natural compounds in cancer therapy 2001.
8. Huang M, Lu JJ, Ding J. Natural Products in Cancer Therapy: Past, Present and Future. *Nat Prod Bioprospect.* 2021;11(1):5–13.
9. Shahzadi I, Ali Z, Baek SH, Mirza B, Ahn KS. Assessment of the antitumor potential of umbelliprenin, a naturally occurring sesquiterpene coumarin. *Biomedicines.* 2020;8(5):126.
10. Rashidi M, Ahmadzadeh A, Ziai SA, Narenji M, Jamshidi H. Evaluating cytotoxic effect of nanoliposomes encapsulated with umbelliprenin on 4T1 cell line. *In Vitro Cellular & Developmental Biology-Animal.* 2017;53:7–11.
13. Mohanraj V, Chen Y. Nanoparticles-a review. *Tropical journal of pharmaceutical research.* 2006;5(1):561–73.
11. S.A. Kalele, A.A. Kundu, S.W. Gosavi, D.N. Deobagkar, D.D. Deobagkar, and S.K. Kulkarni, "Rapid detection of Escherichia coli by using antibody-conjugated silver nanoshells", *Small*, vol. 2, no. 3, pp. 335–338, 2006. [http://dx.doi.org/10.1002/sml.200500286] [PMID: 17193045]

12. S. Huo, S. Jin, X. Ma, X. Xue, K. Yang, A. Kumar, P.C. Wang, J. Zhang, Z. Hu, and X.J. Liang, "Ultrasml gold nanoparticles as carriers for nucleus-based gene therapy due to size-dependent nuclear entry", *ACS Nano*, vol. 8, no. 6, pp. 5852-5862, 2014. [<http://dx.doi.org/10.1021/nn5008572>] [PMID: 24824865]
13. S.P. Gubin, *Magnetic Nanoparticles*, 2009. [<http://dx.doi.org/10.1002/9783527627561>] [20] K.N. Thakkar, S.S. Mhatre, and R.Y. Parikh, "Biological synthesis of metallic nanoparticles", *Nanomedicine (Lond.)*, vol. 6, no. 2, pp. 257-262, 2010. [<http://dx.doi.org/10.1016/j.nano.2009.07.002>] [PMID: 19616126]
14. S. Beg, M. Rahman, A. Jain, S. Saini, P. Midoux, C. Pichon, F.J. Ahmad, and S. Akhter, "Nanoporous metal organic frameworks as hybrid polymer-metal composites for drug delivery and biomedical applications", *Drug Discov. Today*, vol. 22, no. 4, pp. 625-637, 2017. [<http://dx.doi.org/10.1016/j.drudis.2016.10.001>] [PMID: 27742533]
15. Ghasemi M, Turnbull T, Sebastian S, Kempson I. The MTT Assay: Utility, Limitations, Pitfalls, and Interpretation in Bulk and Single-Cell Analysis. *Int J Mol Sci.* 2021;22(23). 25. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *CA: a cancer journal for clinicians.* 2020;70(6):443-59.
16. T.P. Sari, B. Mann, R. Kumar, R.R.B. Singh, R. Sharma, M. Bhardwaj, and S. Athira, "Preparation and characterization of nanoemulsion encapsulating curcumin", *Food Hydrocoll.*, vol. 43, pp. 540-546, 2015. [<http://dx.doi.org/10.1016/j.foodhyd.2014.07.011>]
17. Azimi F, Sanaei M, Rahimzadeh S, Ajideh R, Shahverdi AR, Yazdi MH. Effect of ursolic acid, selenium nanoparticles, and their combination on the metastasis-associated gene expression in MDA-MB-231 breast cancer cells: In-vitro study. 2023.
18. Medina-Cruz D, Truong LB, Sotelo E, Martínez L, González MU, Huttel Y, et al. Bacterial-mediated selenium nanoparticles as highly selective antimicrobial agents with anticancer properties. *RSC Sustainability.* 2023;1(6):1436-48.
19. Gkionis L, Kavetsou E, Kalospyros A, Manousakis D, Garzon Sanz M, Butterworth S, et al. Investigation of the cytotoxicity of bioinspired coumarin analogues towards human breast cancer cells. *Molecular Diversity.* 2020;24:533-41.
20. Rashidi M, Ahmadzadeh A, Ziai SA, Narenji M, Jamshidi H. Evaluating cytotoxic effect of nanoliposomes encapsulated with umbelliprenin on 4T1 cell line. *In Vitro Cell Dev Biol Anim.* 2017;53(1):7-11.