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CARBON NANOTUBES IN DELIVERY OF ANTICANCER HERBAL DRUGS

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ABSTRACT

Malignancy is assessed to be a huge medical issue of the 21st century. The circumstance gets much harder with regards to its treatment utilizing chemotherapy utilizing synthetic anticancer atoms with various side effects. Recently, there has been a change in outlook toward the selection of herbal medications for the treatment of cancer. Right now, appropriate conveyance framework is basically justified to convey these herbal biomolecules to treat cancer. To accomplish this objective, carbon nanotubes (CNTs) have been generally investigated to convey anticancer herbal drugs with improved therapeutic efficacy and safety. This survey interestingly clarifies the biopharmaceutical, clinical and safety aspects of various anticancer home grown medications conveyed through CNTs with a cross-chat on their results. This audit will fill in as a one-stop-look for the perusers on different anticancer herbal medications conveyed through CNTs as a cutting edge futuristic delivery device.

KEYWORDS: Carbon nanotubes, Cancer, Anti-Cancer Herbal Drugs.

INTRODUCTION

1. Cancer

Cancer is an ailment during which there's the uncontrolled growth of abnormal cells by overlooking the normal cellular division cycle.[1] the method in cancer involves irregular cellular growth, by the development of a network of latest blood capillaries, in other words, angiogenesis, and triggered by various signals from cancer tissues which include, mechanical stress, inflammatory responses and mutations.[2]

Development of cancer depends on external factors like tobacco, environmental factors like chemicals, radiation, infectious organisms and elements within the cell-like genetic defects, hormonal changes, immune conditions and mutations, which altogether lead to abnormal cell behaviour and excessive proliferation.[3]

2. Carbon nanotubes

Carbon nanotubes (CNT) belong to a new class of nanomaterials that have unique chemical, physical and biological properties. Structurally, all CNTs can be considered carbon allotropes with a cylindrical architecture. In addition to their unique shape and morphology, the CNTs demonstrate an excellent ability to conduct electronic and thermal energy. These characteristics have made CNTs an ideal candidate for countless applications in various fields, such as electronics, chemistry, optics and biomedicine.[4-8]

3. Herbal Drugs in Cancer Treatment

Plants have been a promising source for the treatment of various diseases, due to the therapeutic activity, fewer side effects than synthetic molecules. Herbal drugs are known to influence various mechanisms, including regulation of gene expression, cell cycle progression, cell proliferation, metabolism and apoptosis.[9]

The anticancer compounds are divided into several classes according to the basic rest in their structure, such as anthracyclines, enediynes, indocarcarbazoles, isoprenoids, polyketide macrolides, glycopeptides, among others. Polyketides are produced by bacteria and fungi that include many drugs, one of which is PTX.[10]

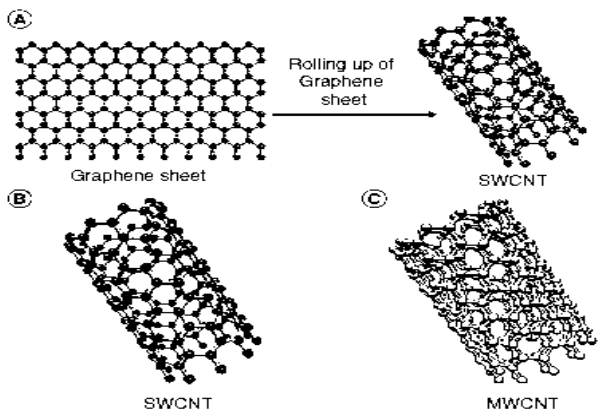
Class	Name of Drugs	Mechanism of Action
Enediynes	Calicheamicin, Dynemicin A, Esperamicin, Kerdarcidin and Neocarzinostatin	Interferes with DNA[11]
Vinca alkaloids	Vincristine, Vinblastine, Vinorelbine and Vindesine are Monoterpene indole alkaloids[12]	Prevent spindle formation in dividing cells[13]
Camptothecin analogs	Camptothecin, Irinotecan and Topotecan	DNA Topoisomerase Inhibitor.[14]
Taxanes	Docetaxel are Diterpene	Inhibit microtubule formation[15]
Podophyllotoxin derivatives	Etoposide and Teniposide	Topoisomerase II inhibitor[16]
Saffron	Carotenoid, Crocetin, Crocin, Safranal and Picrocrocin	Antioxidant property could prevent DNA, RNA and protein damage[17]
Curcumin	Curcumin	Inhibit of cell proliferation and reactive oxidative species, promotion of apoptosis by inhibiting different intracellular transcription factors[18] [19]
Ginseng derivatives	Ginsenosides, Panaxadiols and Panaxatriols	different pharmacological activity.[20]
Terpenoids	Monoterpenoid, Diterpenoid, Triterpenoid, Sesquiterpenoid, etc[21]	Antiapoptotic, Autophagy[22]

CNT: Structure, Properties, & Synthesis

CNTs are needle-shaped tubular structures that act as carriers of various drugs, proteins, genes, among others. Both the functionalization and the conjugation of these CNTs make the charged molecules more soluble and biocompatible, allowing targeting to specific sites.[23]

CNT structure

CNTs are a graphite sheet which is wrapped in the shape of a tube to form single-walled carbon nanotubes (SWCNT) and multiple-walled carbon nanotubes (MWCNT). SWCNTs are cylindrical in shape with a graphene sheet wrapped to form a tube, while multiple-walled nanotubes (MWNT) are made up of multiple laminated layers (concentric tubes) of graphene, although their diameter and length differ from SWCNT and differ in its properties too much.[24]



Properties of CNT

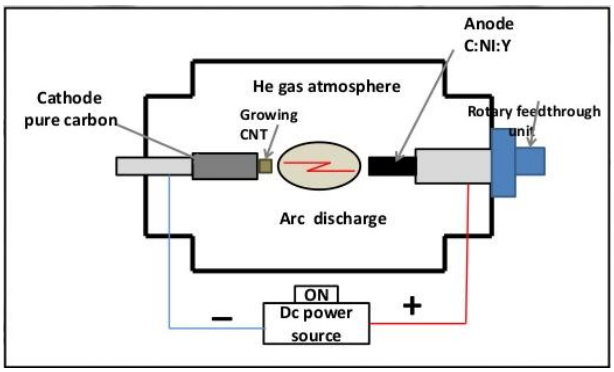
CNTs generally shown to have a high surface area, large aspect ratios and unique mechanical strength. It is known that tensile strength of CNT is almost 100-times greater than that of steel, and also shows electrical and thermal conductivity properties as those of copper.[25]

Synthesis of CNT

There are different methods to synthesize CNT which are listed below.

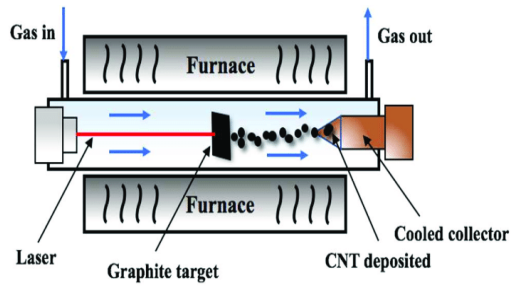
(a) Arc Discharge Method

The production of CNT requires three main components, namely. Carbon feed, metal catalyst, heating source. In this technique, two graphite electrodes are placed in an inert He atmosphere and the DC is passed through it. It is observed that the anode is consumed and the material is formed in the cathode, thus forming the CNT.[26]



(b) Laser Ablation

In this technique, a pulsed laser vaporizes a graphite target in a very high temperature reactor while an inert gas is added to the chamber. As the material, which is vaporized, cools rapidly, causing condensation to form in groups. From these groups, tubular molecules grow in SWCNT until the catalyst becomes large enough to cool the environment, so that carbon can no longer spread through the catalyst surface. Therefore, when vaporized carbon condenses on the colder surface of the reactor, CNT are formed.[27]



(c) Thermal synthesis process

In this method, only thermal energy is fundamentally responsible for the synthesis, and the temperature of the reaction goes up to 1200◦C. Thermal synthesis itself is a very broad term to include various CVD methods, which includes processes in CVD method, carbon monoxide synthesis and flame synthesis.[28]

(d) Chemical vapour deposition

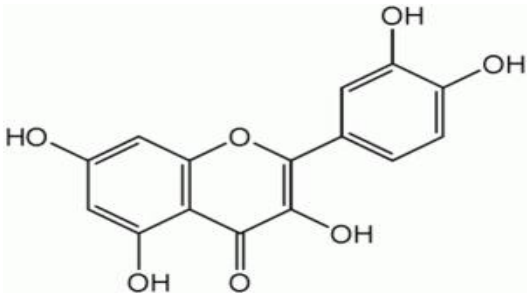
In CVD, the substrate is prepared with a layer of metallic catalyst particles, the most used metals are nickel, cobalt, iron or a combination. The diameters of the CNT thus formed are related to the size of the metal particles. In CVD, the substance could be heated to a temperature of 700 ° C.

Now to start further the growth of nanotubes; At least two gases are introduced into the reactor, such as ammonia, nitrogen or carbon-containing gas, such as methane and ethane. The carbon-containing gas separates on the surface of the catalyst particle and the carbon moves to the edges of the catalyst. the particle eventually leads to the formation of nanotubes.[29]

Anticancer drug delivery: herbal drug loaded in CNTs

Herbal medicines can be loaded into the CNT or adhere to the external surface of the CNT. CNTs can also be combined with conjugated agents, for effective delivery to the target site, reducing the problem of drug loss and off-target effects.[30]

QUERCETIN



Quercetin is (3, 3_, 4_, 5, 7-pentahydroxyflavone) excreted from the air-dried part of the **Spohora japonica L. (Fabaceae)** plant mainly from the bark and leaf, also available in particular fruits like citrus and vegetables, Apple, onion, parsley, green tea, olive oil, grapes, cherry, black mulberry, blackberry and raspberry are the main dietary resources that contain quercetin.[31]

Quercetin shows its anticancer effects through multiple mechanisms, such as antioxidation (through free hydroxyl groups), antiproliferation, cell cycle arrest, apoptosis and angiogenesis.[32]

In addition to the antioxidant activity, its apoptosis and its tumor suppression activity are responsible for the anti-tumor effect. The oxidative activity allows the release of signs of promotion of death through the inhibition of kinase by quercetin, thus improving cell death.[33]

Methods of quercetin delivery by SWCNT into cancer cells

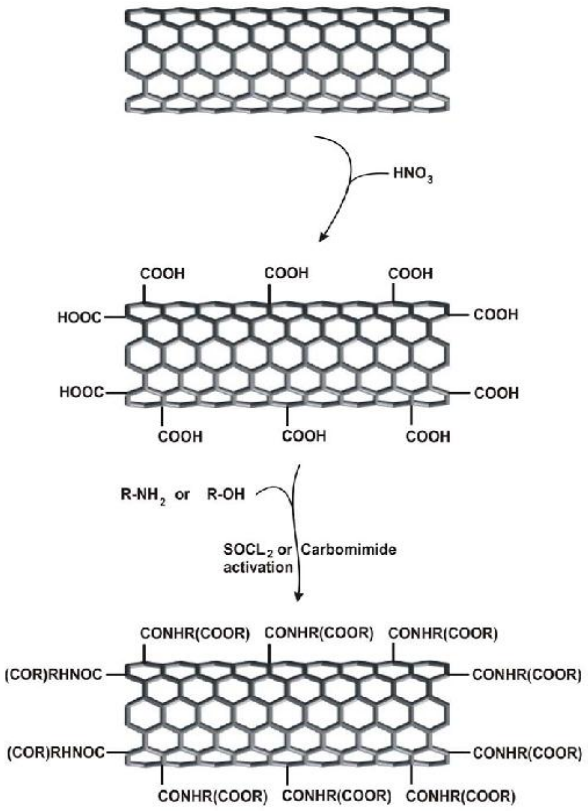
1. Functionalization of SWCNTs With PEG

SWCNT functionalized with polyethylene glycol (PEG) will be prepared with the covalent method. Therefore, to produce the carboxylic terminal, the SWCNTs must be exposed to nitric acid (HNO3) for 24 hours and the acid must be removed by repeated filtering. The pEGylation of carboxylic acid groups in SWCNT will be obtained by adding 1 mM terminated with amine, poly (ethylene oxide) to four members in SWCNT solution in the presence of 1-ethyl-3- [3-dimethylaminopropyl hydrochloride] - Carbodiimide 2mM under light sonication.

After an overnight reaction, the unreacted reagents can be removed by repeated filtration and resuspension of cEGalely PEGylated SWCNTs. These functionalizing groups increase the solubility and biocompatibility of carbon nanotubes.[34, 35]

2. Quercetin loading into functionalized SWCNT

Loading of the quercetin in SWCNT functionalized with RGD-PEG will be performed simply by mixing the quercetin with SWCNT functionalized with RGD-PEG overnight. Unbound excess quercetin can be removed by filtration and washed thoroughly with water (more than 10 times). The functionalization of these nanocomposites was confirmed by Raman spectroscopy, attenuated total reflection (ATR) -FTIR and thermogravimetric analysis (TGA).[36]



3. Quercetin release from SWCNT

Controlled release of drugs from a drug carrier complex is an important aspect of drug delivery systems.[37] Due to the acidic nature of extracellular tissues of tumors and intracellular lysosomes and endosomes, the pH-dependent drug release from SWCNTs could be used for drug release applications that could facilitate the active release of drugs from delivery vehicles. by SWCNT. In an appreciable release solution of acid quercetin from SWCNT Hipco attributed to the increased hydrophilicity and solubility of quercetin at this pH. Where quercetin can be released after reduction in a low pH environment within cancer cells.[38,39]

4. Mechanisms of CNTs uptake by cells

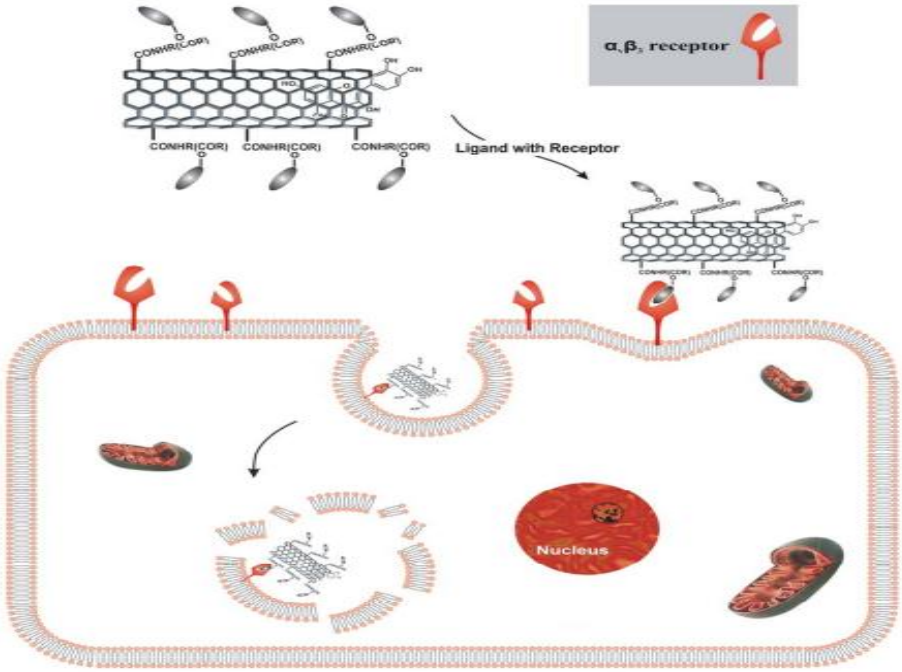
CNTs have the potential of crossing cell membranes which makes them efficient material for drug and gene delivery techniques. The first requirement for drugs delivery to cells is that the drugs should be attached to the drug delivery system by covalent or non-covalent bonding. After getting the targeted organs, tissues or cells,

There are two options
(1) the drug is internalized (i.e., penetrate the cells) without internalization of the carrier or
(2) both the drug and the carrier are internalized.[40-42]

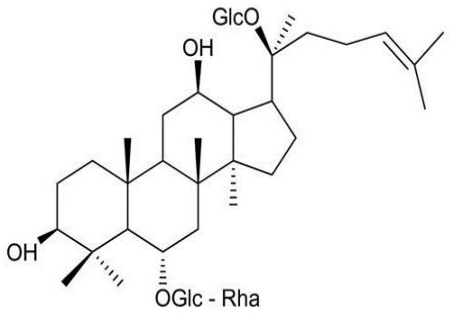
The second internalization method has a more efficient release system because after penetration into the cells, the intracellular environment will help the degradation of the drug-vector conjugate or the release of drug molecules inside the cells, but in the first internalization technique , the extracellular environment facilitates the drug carrier. degradation of conjugates and the drug will pass the lipid membrane to enter the cells.[100]

There are five methods to internalize macromolecules or nanoparticles in mammalian cells.

- Phagocytosis,
- macro-pinocytosis,
- clathrin-mediated endocytosis,
- caveolin mediated path-ways, and
- clathrin/caveolin-independent endocytosis.[40, 43,44]



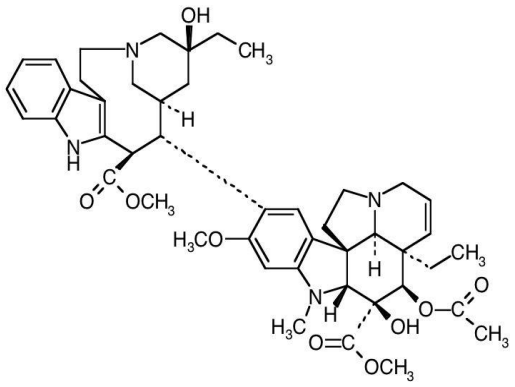
GINSENOSIDE



- Ginsenoside is obtained from *Panax ginseng*, Araliaceae, a herb found in Chinese medicine, and was first isolated in 1963. Ginseng is known for its immunomodulatory and metabolism actions, as well as blood pressure control.[45]
- Among the complex components of ginseng, ginsenosides (also known as ginseng saponins or triterpene saponins) are the main components responsible for the biochemical and pharmacological actions of ginseng.[46, 47-49]
- Ginsenosides are triterpene saponins formed from the skeleton of dammarane (17 coals in a four-ring structure) together with sugar residues.[50] Due to the presence of ginsenoside saponin, ginseng shows its anticancer effect.[51]
- Ginsenoside exerts their anticancer effects by the diverse molecular mechanism of actions which includes modulation in various signalling pathways such as regulation of proliferative cell mediators, various growth factors, Tumor suppressors, oncogenes, cell death mediators, protein kinases[52], activation of caspase- 3, caspase-8 and caspase-9.[53]

- MWCNTs were synthesized through catalytic chemical vapor deposition technique, with a diameter of 15–40 nm.[54] The prepared CNTs were oxidized by nitric acid and sulfuric acid, and then a solution of ginsenoside (Rb1, Rg1) with N-(3-Dimethylaminopropyl)-N-ethyl carbodiimide hydrochloride was added to oxidized CNTs. This reaction is called as EDC coupling.

VINBLASTINE



- Vinblastine, a vinca alkaloid derived from the periwinkle plant Catharan therefore roseus, is an indole rich alkaloid containing catharanthine and vindoline.
- Vinblastine, at low concentrations, inhibits growth and shortening of microtubules and at high concentrations hinder the polymerization of microtubules.[55]
- The stable orientations of vinblastine with respect to the CNT courier, and its effect of the temperature change and of the CNT structure in different systems with vinblastine molecules (loaded with tubular chair, chiral and zigzag structures) with non-functionalized and functionalized with ester.
- Functionalization is performed to reduce the toxicity of CNTs and to improve biocompatibility with biological systems and to improve the VLB-CNT interactions of a longer CNT with a higher load capacity.[56]

FUTURE PRESPECTIVES

- ❖ CNTs have tremendous scope for exciting research and technology development in the field of healthcare as a delivery platform for bio molecules.
- ❖ The use of CNT in the development of sanitary products can be obtained using a combination of different CNT properties, as seen above, while some of the most exclusive properties, such as thermal conductivity, modulation of the properties of encapsulated species and mechanical photoacoustic movement remain unexplored in the biological field.
- ❖ On the contrary, there are areas of biology where CNTs have not yet been used to provide a unique function, but could be useful, such as interfacing cascades of biochemical reactions and signaling and recognizing cells.

CONCLUSION

- ❖ we observed that delivery of the herbal anticancer drug through CNTs is of a great advantage regarding selectivity, tumour uptake and inhibition of growth, loss of cell viability, etc. Moreover, upon result analysis of the data of various drugs such as quercetin, ginsenoside & Vinblastine.
- ❖ The trend in current time is high for the herbal based anticancer treatment and is increasing day by day. Owing to its excellent properties, CNTs provides greater degree of encapsulation of drugs inside the tube, surface loading of the drug is also possible. Therefore, the advantage of CNTs and the herbal drugs give a dual benefit, in other words, penetration of the herbal drug into the desired target with the help of CNTs is achieved for the treatment of cancer.

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REFERENCES

1. Tekade RK, Sun X. The Warburg effect and glucose-derived cancer theranostics. Drug Discov. Today, 2017; 22(11): 1637–1653.
2. Orgogozo V, Morizot B, Martin A. The differential view of genotype–phenotype relationships. Front. Genet, 2015; 6: 79.
3. Dy GW, Gore JL, Forouzanfar MH, Naghavi M, Fitzmaurice C. Global burden of urologic cancers, 1990–2013. Eur. Urol, 2017; 71(3): 437–446.
4. Ramalingame, R.; Lakshmanan, A.; Muller, F.; Thomas, U.; Kanoun, O. Highly sensitive capacitive pressure sensors for robotic applications based on carbon nanotubes and PDMS polymer nanocomposite. J. Sens. Sens. Syst, 2019; 8: 87–94.
5. Lin, J.N.; Yeh, C.Y.; Pan, Y.N.; Lin, M.C.; Fan, F.Y. E_ect of carbon nanotubes on in vitro cellular responses for bioglass application. Mater. Lett, 2019; 235: 141–143.
6. Filatzikioti, A.; Glezos, N.; Kantarelou,V.; Kyriakis, A.; Pilatos, G.; Romanos, G.; Speliotis, T.; Stathopoulou, D.J. Carbon nanotube Schottky type photodetectors for UV applications. Solid State Electron, 2019; 151: 27–35.
7. Muhulet, A.; Miculescu, F.; Voicu, S.I.; Schutt, F.; Thakur, V.K.; Mishra, Y.K. Fundamentals and scopes of doped carbon nanotubes towards energy and biosensing applications. Mater. Today Energy, 2018; 9: 154–186.
8. Rahman, G.; Najaf, Z.; Mehmood, A.; Bilal, S.; Shah, A.; Mian, S.; Ali, G. An Overview of the Recent Progress in the Synthesis and Applications of Carbon Nanotubes. C, 2019; 5: 3.
9. Turkson J. Cancer drug discovery and anticancer drug development. In: The Molecular Basis of Human Cancer. Springer, NY, USA, 2017; 695–707.
10. McCarthy FO, Winfield HJ, O'Shea KD, Cahill MM, Pierce LT.Arresting cell growth by novel functionalised indolocarbazoles. In: 1st International Electronic Conference on Medicinal Chemistry. Eynde J (Ed.). Multidisciplinary Digital Publishing Institute, Basel, Switzerland, 2015.
11. Guo X-F, Zhu X-F, Cao H-Y et al. A bispecific enediyne-energized fusion protein targeting both epidermal growth factor receptor and insulin-like growth factor 1 receptor showing enhanced antitumor efficacy against non-small-cell lung cancer. Oncotarget, 2017; 8(16): 27286.
12. Mhaidat N, Alzoubi K, Khabour O et al. Assessment of genotoxicity of vincristine, vinblastine and vinorelbine in human cultured lymphocytes: a comparative study. Balkan J. Med. Genet, 2016; 19(1): 13–20.
13. Safe S, Kasiappan R. Natural products as mechanism-based anticancer agents: Sp transcription factors as targets. Phytother. Res, 2016; 30(11): 1723–1732.
14. Li F, Ling X, Harris DL et al. Topoisomerase I (Top1): a major target of FL118 for its antitumor efficacy or mainly involved in its side effects of hematopoietic toxicity? Am. J. Cancer Res, 2017; 7(2): 370.
15. Liu Z, Zhang T, Tang C, Yin C. Amphiphilic nanoparticles based on poly (vinyl pyrrolidone) and stearoyl modified chitosan as drug vehicles for paclitaxel delivery. Mater. Lett, 2016; 185: 226–229.
16. Amelio I, Lisitsa A, Knight RA, Melino G, Antonov AV. Polypharmacology of approved anticancer drugs. Curr. Drug Target, 2017; 18(5): 534–543.
17. Tuberoso CI, Rosa A, Montoro P, Fenu MA, Pizza C. Antioxidant activity, cytotoxic activity and metabolic profiling of juices obtained from saffron (Crocus sativus L.) floral by-products. Food Chem, 2016; 199: 18–27.
18. Landeros JM, Belmont-Bernal F, P´erez-Gonz´alez AT et al. A two-step synthetic strategy to obtain a water-soluble derivative of curcumin with improved antioxidant capacity and in vitro cytotoxicity in C6 glioma cells. Mater. Sci. Eng. C, 2017; 71: 351–362.
19. Chen J, He Z-M, Wang F-L et al. Curcumin and its promise as an anticancer drug: an analysis of its anticancer and antifungal effects in cancer and associated complications from invasive fungal infections. Eur. J. Pharm, 2016; 772: 33–42.
20. Wang W, Zhao Y, Rayburn ER, Hill DL, Wang H, Zhang R. In vitro anti-cancer activity and structure–activity relationships of natural products isolated from fruits of Panax ginseng. Cancer Chem. Pharm, 2007; 59(5): 589–601.
21. Huang M, Lu J-J, Huang M-Q, Bao J-L, Chen X-P, Wang Y-T. Terpenoids: natural products for cancer therapy. Expert Opin. Invest. Drugs, 2012; 21(12): 1801–1818.
22. Zhang DM, Xu HG, Wang L et al. Betulinic acid and its derivatives as potential antitumor agents. Med. Res. Rev, 2015; 35(6): 1127–1155.
23. ChopdeyPK, Tekade RK, Mehra NK, Mody N, Jain NK. Glycyrrhizin conjugated dendrimer and multi-walled carbon nanotubes for liver specific delivery of doxorubicin. J. Nanosci. Nanotechnol, 2015; 15(2): 1088–1100.
24. De Volder MF, Tawfick SH, Baughman RH, Hart AJ. Carbon nanotubes: present and future commercial applications. Science, 2013; 339(6119): 535–539.
25. Behabtu N, Young CC, Tsentalovich DE et al. Strong, light, multifunctional fibers of carbon

nanotubes with ultrahigh conductivity. Science, 2013; 339(6116): 182–186.
26. Yan X, Gu J, Zheng G et al. Lowly loaded carbon nanotubes induced high electrical conductivity and giant magnetoresistance in ethylene/1-octene copolymers. Polymer, 2016; 103: 315–327.
27. Krestinin A, Kiselev N, Raevskii A, Ryabenko A, Zakharov D, Zvereva G. Perspectives of single-wall carbon nanotube production in the arc discharge process. Eurasian Chem. Tech. J, 2017; 5(1): 7–18.
28. Chrzanowska J, Hoffman J, Ma-lolepszy A et al. Synthesis of carbon nanotubes by the laser ablation method: effect of laser wavelength. Phys. Status Solidi (B), 2015; 252(8): 1860–1867.
29. Li DJ, Maiti UN, Lim J et al. Molybdenum sulfide/N-doped CNT forest hybrid catalysts for high-performance hydrogen evolution reaction. Nano Lett, 2014; 14(3): 1228–123.
30. Golshadi M, Maita J, Lanza D, Zeiger M, Presser V, Schrlau MG. Effects of synthesis parameters on carbon nanotubes manufactured by template-based chemical vapor deposition. Carbon, 2014; 80: 28–39.
31. Bonif´acio BV, da Silva PB, dos Santos Ramos MA, Negri KMS, Bauab TM, Chorilli M. Nanotechnology-based drug delivery systems and herbal medicines: a review. Int. J. Nanomed, 2014; 9: 1.
32. S.B. Bukhari, S. Memon, M.M. Tahir, and M.I. Bhanger, "Synthesis, characterization and antioxidant activity copper-quercetin complex," Spectrochim Acta A, 2009; 71: 1901-1906.
33. Roleira FM, Tavares-da-Silva EJ, Varela CL et al. Plant derived and dietary phenolic antioxidants: anticancer properties. Food Chem, 2015; 183: 235–258.
34. Seo H-S, Ku JM, Choi H-S et al. Quercetin induces caspase-dependent extrinsic apoptosis through inhibition of signal transducer and activator of transcription 3 signaling in HER2-overexpressing BT-474 breast cancer cells. Oncol. Rep, 2016; 36(1): 31–42.
35. Z. Liu, X. Sun, N. Nakayama-Ratchford, and H. Dai, "Supramolecular chemistry on water-soluble carbon nanotubes for drug loading and delivery," ACS Nano, Aug 2007; 1(1): 50-6.
36. Z. Liu, K. Chen, C. Davis, S. Sherlock, Q. Cao, X. Chen, and H. Dai, "Drug delivery with carbon nanotubes for in vivo cancer treatment," Cancer Res, vol. 68, (no. 16), pp. 6652-60, Aug 15 2008.
37. T.M. Allen and P.R. Cullis, "Drug delivery systems: entering the main stream," Science, 2004; 303: 1818-1822.
38. Z. Liu, A.C. Fan, K. Rakhra, S. Sherlock, A. Goodwin, X. Chen, Q. Yang, D.W. Felsher, and H. Dai, "Supramolecular stacking of doxorubicin on carbon nanotubes for in vivo cancer therapy," Angew Chem Int Ed Engl, 2009; 48(41): 7668-72.
39. J. Chen, S. Chen, X. Zhao, L.V. Kuznetsova, S.S. Wong, and I. Ojima, "Functionalized single-walled carbon nanotubes as rationally designed vehicles for tumor-targeted drug delivery," J Am Chem Soc, Dec 10 2008; 130(49): 16778-85.
40. P.A. Tran, L. Zhang, and T.J. Webster, "Carbon nanofibers and carbon nanotubes in regenerative medicine," Adv Drug Deliv Rev, Oct 5 2009.; 61(12): 1097-114.
41. M. Prato, K. Kostarelos, and A. Bianco, "Functionalized carbon nanotubes in drug design and discovery," Acc Chem Res, Jan 2008; 41(1): 60-8.
42. T. Crouzier, A. Nimmagadda, M.U. Nollert, and P.S. McFetridge, "Modification of single walled carbon nanotube surface chemistry to improve aqueous solubility and enhance cellular interactions," Langmuir, Nov 18 2008; 24(22): 13173-81.
43. Y. Yu, Q. Zhang, Q. Mu, B. Zhang, and B. Yan, "Exploring the Immunotoxicity of Carbon Nanotubes," Nanoscale Res Lett, 2008; 3; 271–277.
44. Y. Omidi and M. Gumbleton, "Biological membranes and barriers," in Biomaterials for Delivery and Targeting of Proteins Nucleic Acids, E. Mahato RI ed., NewYork: CRC Press, 2005; 232-274.
45. Shergis JL, Zhang AL, Zhou W, Xue CC. Panax ginseng in randomised controlled trials: a systematic review. Phytother. Res, 2013; 27(7): 949–965.
46. Attele AS, Wu JA, Yuan CS: Multiple pharmacological effects of ginseng. Biochem Pharmacol, 1999; 58: 1685-1693.
47. Lee SJ, Sung JH, Moon CK, Lee BH: Antitumor activity of a novel ginseng saponin metabolite in human pulmonary adenocarcinoma cells resistant to cisplatin. Cancer Lett, 1999; 144 (1): 39-43
48. Xie JT, Shao ZH, Vanden Hoek TL, Chang WT, Li J, Mehendale S, Wang CZ, Hsu CW, Becker LB, Yin JJ: Antioxidant effects of ginsenoside Re in cardiomyocytes. Eur J Pharmacol, 2006; 532(3): 201-207.
49. Qi LW, Wang CZ, Yuan CS: American ginseng: potential structure-function relationship in cancer chemoprevention. Biochem Pharmacol, 2010; 80(7): 947-954.
50. Patel S, Rauf A. Adaptogenic herb ginseng (Panax) as medical food: Status quo and future prospects. Biomed. Pharm, 2017; 85: 120–127.
51. Wong AS, Che C-M, Leung K-W. Recent advances in ginseng as cancer therapeutics: a functional and mechanistic overview. Nat. Prod. Rep, 2015; 32(2); 256–272.
52. Li J, Wei Q, Zuo G-W et al. Ginsenoside Rg1 induces apoptosis through inhibition of the EpoR-mediated JAK2/STAT5 signalling pathway in the TF-1/Epo human leukemia cell line. Asian Pac. J. Cancer Prev, 2014; 15(6): 2453–2459.
53. Park E-H, Kim Y-J, Yamabe N et al. Stereospecific anticancer effects of ginsenoside Rg3 epimers isolated from heat-processed American ginseng on

human gastric cancer cell. J. Ginseng Res, 2014; 38(1): 22–27.
54. Lahiani MH, Dervishi E, Chen J et al. Impact of carbon nanotube exposure to seeds of valuable crops. ACS Appl. Mater. Interfaces, 2013; 5(16): 7965–7973.
55. Moudi M, Go R, Yien CYS, Nazre M. Vinca alkaloids. Int. J. Prev. Med, 2013; 4(11): 1231.
56. Li Z, Tozer T, Alisaraie L. Molecular dynamics studies for optimization of noncovalent loading of vinblastine on single-walled carbon nanotube. J. Phys. Chem. C, 2016; 120(7): 4061–4070.