Indian Journal of Biotechnology and Pharmaceutical Research 1 (2):1-8 ***Dec.*** *2013/Article. ISSN 2347-3266*

Ethnomedicinal drug discovery for cancer through accumulated facts and novel drug delivery systems - a review

PRIYAM SINGH[1*], RAJNI SHRIVASTAVA[2], MANIK SHARMA[3], MATADEEN BHARTI[4]

[1]Dept. of Zoology, SSL Jain College, Vidisha (M.P.),
[2]Dept. of Zoology, Govt. BHEL College, Bhopal (M.P.),
[3]Bhoj Mahavidyalaya, Bhopal (M.P.),[4]Dept. of Zoology, Govt. College, Jatara (M.P.)

ABSTRACT

Plants have revealed to be a good source for a variety of bioactive constituents for various ailments. Cancer is a public health problem worldwide. Medicinal herbs proved best natural anticancer remedies. Novel drug delivery systems have benefits of improved therapy by increasing the efficiency of phytoconstituents and improved targeting. Optimization of the importance of drug leads now requires multidisciplinary collaboration and to step start for target oriented researches of the phytocomponents for treatment of cancer to launch the sure cure for appropriate treatments.

Key words: cancer, phytoconstituents, novel drug delivery systems, drug leads

Cancer is the second leading cause of death worldwide. It accounted for 7.6 million deaths i.e. around 13% of all deaths in 2008 according to World Health Organization (WHO). Based on GLOBOCAN 2008 estimates about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008 (journal A). It is a major cause of mortality and morbidity in developing as well as in developed countries. Besides advances in medicine it is still a major public health problem. Melanoma incidence is among the top ten of leading cancer sites in the United States (US) with a fifth place for men and a sixth place for women (Cancer facts and Figures 2012). Moreover, based on the years lost to cancer, melanoma would merit a higher ranking because relatively young people are affected by this malignancy (GLOBACAN 2010; Albert et al. 1990; Osterlind 1992). The WHO has estimated that approximately 80% of the world's population depends on traditional medicines for meeting their primary health care needs (Brochez et al. 1999). In spite of advances in medicine, still there is no reliable cure for melanoma. So this deadly disease demands attention from investigators worldwide.

Indigenous plants have been selected and used empirically as drugs for centuries initially as traditional preparations then as pure active principles, with this knowledge and accumulated practice passing from generation to generation (Taylor et al. 2001). Further increasing reliance on the use of medicinal plants in the industrialized societies has been traced to the extraction and development of several drugs and chemotherapeutics from these plants as well as from traditionally used rural herbal

*Corresponding Author: **priyam.singh32@gmail.com**

remedies (UNESCO 1998). Medicinal plant drugs can be placed into two broad categories. Firstly, they are included in complex mixtures containing a wide variety of compounds and secondly they are used as pure, chemically defined active principles (Hamburger and Hostettmann 1991). Chemotherapy, being a major treatment modality used for the control of advanced stages of malignancies and as a prophylactic against metastasis, exhibits severe toxicity on normal tissues (Pandey et al 2006). The ethnopharmacological approach for the search of new anticancer agents from the plant sources has proved to be more predictive. There are many natural substances which exhibits antitumor activities.

The active ingredients of plant extract used are chemicals that are similar to those in purified medications. Further the amount of information on the relative safety of herbal remedies is limited. There is lack of use of standard and measured doses and large volume of doses are difficult to manage. Glycosides, flavonoids, tannins and alkaloids have hypoglycemic activities (Jing et al. 2007). Flavonoid compounds especially quercetin and genistein have antitumor activity. These compounds are cytotoxic to cancer cells but have no or insignificant activity in normal cells (Cherian and Augusti 1995). It has been reported that flavonoid, apigenin holds great promise as a chemopreventive agent for a variety of cancers and exhibits significant activity against UV induced DNA damage and thus protect against skin cancer (Pouget et al. 2001). It also inhibits the growth of a variety of human cancer cells including leukemia, breast, colon, skin, thyroid and prostate cancers (Baliga and Katiyar 2006).

Flavonoids and tannins are phenolic compounds and plant phenolics are a major group of compounds that act as primary antioxidants of free radical scavengers (Khan and Sultana 2006). These polyphenolic compounds display a remarkable spectrum of biological activities including those that might be able to influence processes that are deregulated during cancer development. They may therefore have beneficial health effects and can be considered possible chemopreventive or therapeutic agents against cancer (Polterait 1997; Birt et al. 2001).

Facts for Ethnomedicinal values of Indigenous Plants

Methanolic extract of *Moringa oleifera* showed *in vitro* cytotoxicity against lung (A-549), colon (502713HT-29) and neuroblastoma (IMR-32) human cancer cell lines (Shaban et al. 2012). Methanolic extract of *Rubia cardifolia* and *Plumbago zeylanica* showed 50% MCF-7 cell line inhibition (Aditya et al. 2013). Extracts of *Trailliaedoxa gracilis* showed a dose dependent reduction of proliferation and induction of apoptosis in the KRJ-I cells. It also showed tumor growth inhibition in heterotransplanted SCID mice (Severe Combined Immuno Defiency) (Swejda et al. 2010).

Acetone extract of *T. procumbens* flower was reported to possess 82.28% cancer cell death against human prostate epithelial cell line PC3 (Vishnupriya et al. 2011). The aqueous extract of *Centella asiatica* showed antitumor potential against B6F10 melanoma cell lines which showed increased activity in life span of treated mice C57BL. The extract significantly reduced the tumor volume (Rai et al. 2011). Methanolic extract of *Cucurbita maxima* showed anticancer activity against Ehrlich ascites carcinoma. The anticancer activity may be due to its cytotoxicity and antioxidant properties (Saha et al. 2011).

Mechanisms of actions of Phytoconstituents

Cancer cells exhibit deregulation in multiple cellular signalling pathways, yet all cancers share a number of common hallmark capabilities, such as genetic instability, self-sufficiency in growth signals, insensitivity to antigrowth signals, avoidance of apoptosis, unlimited replication, sustained angiogenesis and tissue invasion and metastasis (Ziech et al. 2012).

Apigenin exhibits antiproliferative effects and proapoptotic activities through caspase-3 activation (DU-145) and breast (MDA-MB-237) cancer cells expressing only estrogen receptor (ER) ß meaning that anticancer action of apigenin is mediated in part by ER ß (Mak et al. 2006). Therefore, utilizing specific agents to target single pathways is a tactic that frequently fails in cancer therapy. Genetic instability produces intra-tumoral heterogeneity that enables adaptive resistance. Combination chemotherapy that targets a number of distinct molecular mechanisms is therefore preferable and considered more promising, but the use of multiple agents is often constrained due to corresponding increases in toxicity (Sarkar and Li 2009).

Identification of Bioactive components

With the development of analysis technologies such as gas chromatography (GC), High Performance Column Chromatography (HPLC), Mass (MS) one can determine precise quantity range of the active components in the botanical drug products. The pure compounds, extracts or purified fractions attained US patent (Feng et al. 2011). HPLC purified fraction of alcohol extract of Chinese herbal plant Artemisia dependent increase of cell growth inhibition for A375 melanoma cells. The active fraction determined to contain a flavonoid Eupatilin. Eupatilin induces apoptosis and G2/M phase cell cycle arrest in A375 cells (Shawi et al. 2011).

Development of Novel Drug Delivery Systems

With the development of novel drug delivery system therapeutics of plant origin can be proved better than conventional usages. A targeted drug delivery system offers the potential to enhance the therapeutic index of anticancer agents either by increasing the drug concentration in tumor cells or by decreasing the exposure in normal host tissues (Joensuu et al. 2000). Out of many novel drug delivery systems lipoproteins can be used effectively as a targeted drug delivery system in cancer to selectively deliver the compounds and determine its efficacy and further to improve the therapy (Kushwaha et al. 2012). Drugs from plant origin cannot step up due to drug supply issues and thus their trials are limited (Cragg and Newman).

Table 1: *List of Drug Delivery systems to increase the efficiency of bioactive compounds.*

S.No.	Drug delivery systems	Reference
1.	Lipoprotein	27,25,35,36
2.	Nanoparticle	12
3.	Nanoemulsion	26
4.	Microcapsules	17,49,52
5.	Microemulsion	24
6.	Microspheres	26
7.	Dendrimers	26
8.	Phytosomes	32

Patents

Worldwide there are claims for anticancer properties of single pure compounds, extracts or fractions from herbal medicines. Thus there is increasing interest in the identification of molecules associated with plants with properties to inhibit cancer and metastasis. We firstly reported that berberine and coptidis rhizome aqueous extract with anticancer properties by its cell death induction and cell migration inhibition inhibition in cell models of nasopharyngeal

carcinoma and hepatocellular carcinoma (Tsang et al. 2009; Wang et al. 2010). Flavonoid glycosides are reported and patented to be active against hepatocellular carcinoma via inhibition of oxidative stress and polyamine biosynthetic pathway (Saxena et al. 2006).

Table 2: *List of patents for extracts and fractions showing anticancer effect.*

S.No.	Patent No.	Date of Publication	Title	Bioactive Compound	Cancer	Mechanism of action	Reference
1.	US20100009017	01/14/2010	Anticancer Methods Using extracts of *Acacia nilotica* *asphodelaides* Bunge	Extracts of *Acacia nilotica asphodelaides* Bunge	Breast cancer	Apoptosis	10
2.	US20100028472	02/04/2010	Herbal composition and process for its preparation	Extract of *Piper betle* leaves	Leukemia.	Against the BCR-ABL mutated imatinib-resistant cell lines	28
3.	US5709031	05/04/2010	Angiogenic agents from plant extracts, gallic acid, and derivatives	Various derivatives of gallic acid	Various cancer	Antiangiogenesis	18
4.	US20090239090	10/15/2009	Anticancer methods employing extracts of *Abelmoschus moschatus* Linn	Oleanolic acid and sapon in	Breast cancer	Retinoic receptor (RR) negative breast cancer. Apoptosis	11
5.	US7201928	04/10/2007	Extracts of orange peel for prevention and treatment of cancer	Flavone components	Various cancer	Inhibitory effects of cell proliferation	23
6.	US20070082072	04/12/2007	Herbal compositions for treating cancer	6 Herbal composition	Various cancers	Apoptosis	22
7.	US20060280817	12/14/2006	Pharmaceutical composition useful for the treatment of hepatocellular carcinoma	Flavonoid glycosides such as butrin and isobutrin	Hepatocellular carcinoma	Oxidative stress inhibition and polyamine biosynthetic pathway	46
8.	US20030200070	09/22/2005	Compositions of botanical extracts for cancer therapy	Extracts of said 3 herbs, and optionally, *Physalis* *pubescens* (ma buckthorn)	Various cancers	Cytotoxicity, Cox-2 inhibition	15
9.	US20040116394	06/17/2004	Method for treating cancer using betulinic acid rich herbal extract	*Zizyphus*	Various cancer	Apoptosis	34
10.	US6649183	11/18/2003	Herbal formulation	*Tinospora cordifolia* and *Aloe vera* (Aloe barbadensis)	Various cancer	Haematological malignancies	38

Table 3: *List of patents for pure compound showing anticancer effect.*

S.No.	Patent No.	Date of Publication	Title	Bioactive Compound	Cancer	Mechanism of action	Reference
1.	US20100197584	08/05/2010	Use of curcumin to block brain tumor formation in mice	Curcumin and curcumin derivatives	Brain tumor	Prevent tumor formation, tumor cell invasion and tumor metastasis	4
2.	US20100197619	08/05/2010	Cyclin dependent protein kinases inhibitor of Scutellaria flavonoid organic amine derivatives, synthesis and use thereof	Scutellaria flavonoid organic amine derivatives	Various cancer	Apoptosis cyclin-dependent protein kinases (Cdks) inhibitors	58
3.	US7662976	02/16/2010	Triptolide derivatives for modulation of apoptosis and immunosuppression	Triptolide derivatives	Colon cancer, breast cancer, lung cancer and prostate cancer	Modulation of apoptosis and immunosuppression	14
4.	US20090298938	12/03/2009	Use of semi-synthetic analogues of boswellic acids for anti-cancer activity	Analogues of boswellic acids	Various cancer	Apoptosis	42
5.	US7582367	09/22/2009	Compounds from Garcinia henburyi, their use in treating cancer and method of separating Epimers thereof	C-2 epimeric xanthones	Various cancers	Cytotoxicity	21
6.	US7514412	04/07/2009	Anticancer biotigeloyl saponins	Saponins isolated from Xanthoceras sorbifolia	Various cancer		8
7.	US20070298132	12/27/2007	Berberine as selective lung cancer agent	Berberine	Lung cancer	Cytotoxicity	33

CONCLUSIONS

Ethnobotanical importance of the indigenous plants should be explored through using value added drug delivery systems. Many of the extracts showing anticancer activity *in vitro* do not show or less activity *in vivo* because of no proper targeting and thus the *in vitro* bioactive compound is not worked further because of low absorption. To ensure the activity of biological components we should first ensure their proper delivery to the targeted site to action.

Flavonoids make the major composition of food intake and are non toxic so various compositions of different flavonoids should be researched against various cancers to step forward further and to establish its medicinal importance.

However hard we are trying to reveal that bioactive compounds might work in inhibition of cancer at times it can't be helped to be rigorously tested in Phase IV trials for various reasons. But we need to overcome all the barriers. For the same all the data available till date should be recollected and revised to combine the principles and compose a novel combination to overcome the complexities with use of recent advances in various technologies. Till date many compounds are known to possess anticancer property *in vitro* as well as *in vivo* studies. There is a need to further study the effectiveness of the biologically active compounds in more appropriate manner. Plant constituents should be researched through available novel drug delivery system.

ACKNOWLEDGEMENTS

Authors are highly thankful to M.P. Biotechnology Council as a funding source through IMBIBE-JRF (IMAGING BIOTECH BASED ENCOMIUM).

REFERENCES

Aditya VSPK S, Kumar N and Mokkapati A, 2013. Invitro anticancer activities of few plant extracts against MCF-7

and HT-29cell lives. *International Journal of Pharma Sciences,* **3(2):** 185-188.

Albert VA, Koh HK, Geller AC, Miller DR, Prout MN and Lew R A, 1990. Years of potential life lost: another indicator of the impact of cutaneous malignant melanoma on society. *Journal of the American Academy of Dermatology*, **23 (2 Pt 1):** 308-10.

Baliga MS and Katiyar SK, 2006. Chemoprevention of photocarcinogenesis by selected dietary botanicals. *Photochemical and Photobiological Sciences*, **5(2):** 243–53.

Banerjee P and Raja KS, 2010. Use of curcumin to block brain tumor formation in mice. US20100197584.

Birt DF, Hendrich S and Wang W, 2001. Dietary agents in cancer prevention: Flavonoids and isoflavonoids. *Pharmacology and Therapy*, **90(2-3):** 157–77.

Brochez L, Myny K, Bleyen L, De Backer G and Naeyaert JM, 1999. The melanoma burden in Belgium; premature morbidity and mortality make melanoma a considerable health problem. *Melanoma Research,* **9(6):** 614-18.

Cancer facts and Figures, Statistics for 2008 (2012). http://www.cancer.org/www.who.int/ mediacentre/factsheets/fs297/en/cited: 10/1/12

Chan PK, Mak MS and Wang Y, 1997. Anticancer biangeloyl saponins. US7514412.

Cherian S and Augusti KT, 1995. Insulin sparing action of leucopelargonidin derivative isolated from Ficus bengalesis Linn. *Indian Journal of Experimental Biology*, **33:** 608-11.

Cohen I, 2010. Anticancer methods using extracts of *Anemarrhena asphodeloides* bunge. US20100009017.

Cohen I, 2009. Anticancer methods employing extracts of *Gleditsia sinensis* Lam. US20090258096.

Conti M, Tazzaria V, Baccini C, Pertici G, Serino LP and De Georqi U, 2006. Anticancer Drug Delivery with Nanoparticles, *In Vivo*, 20(6A): 697-701.

Cragg GM and Newman DJ, 2005. Drug Discovery and Development from natural products: The Way Forward. 11th NAPRECA Symposium Book of Proceedings, Antananarivo, Madagascar. P-56-69.

Dai D, Musser JH and Lennox ES, 2010. Triptolide derivatives for modulation of apoptosis and immunosuppression. US7662976.

Dao J, Dao TCS, Tong DD, Wilson L, Jordan MA and Gerwick W, 2005. Compositions of botanical extracts for cancer therapy. US20050208070.

Feng Y, Wang N, Zhu M, Feng Y, Li H and Tsao S, 2011. Recent progress on anticancer candidates in plants of herbal medicinal products. *Recent Patenta and Food, Nutrition and Agriculture,* **3:** 30-48.

Garcia-Carbonero R and supko JG, 2002. Current perspectives on the clinical experience, pharmacology and continued development of the camptothecins, *Clinical Cancer Research*, **8:** 641-661.

Greenway FL, 2010. Angiogenic agents from plant extracts, gallic acid and derivatives. US7709031.

GLOBACAN 2008, IARC, 2010.

Hamburger M and Hostettmann K, 1991. Bioactivity in plants: The link between phytochemistry and medicine. *Phytochemistry*. 30: 3864-74.

Han QB, Song JZ, Qiao CF, Yang L and Xu HX, 2009. Compounds from *Garcinia hanburyi*, their use in treating cancer and method of separating epimers therof. US7592367.

Hsieh CF, 2007. Herbal composition for treating cancer. US20070082072.

Huang MT, Ho CT, Rosen RT, Ghai G, Lipkin M, Chen KY, Telang N, Boyd C and Csiszar K, 2007. Extracts of orange peel for prevention and treatment of cancer. US7201928.

Jain J, Fernandes and Patravale V, 2010. Formulation Development of Parental Phospholipid-based Microemulsion of Etopside, *AAPS PharmSciTech*, 11(2): 826-831.

Ji B, Chen W, Lu DR and Halpern DS, 2001. Cell culture and animal studies for intracerebral delivery of borocaptate in liposomal formulation. *Drug delivery*, **8(1):** 13-17.

Jing S, Bao RL, Wen JH, Li-Xia Y and Xiao PQ, 2007. *In vitro* anticancer activity of aqueous extracts and ethanol extracts of fifteen traditional Chinese medicine on human digestive tumor cell line. *Phytotherapy Research*, **21:** 1102-04.

Joensuu H and Tenhunen M, 1999. Physical and Biological targeting of radiotherapy. *Acta Oncology*, 38, **5(2):** 194-199.

Joshi KS, Wagh V and Sharma S, 2010. Herbal composition and process for its preparation. US20100028472.

Khan T H and Sultana S, 2006. Apigenin induces apoptosis in Hep G2 cells: possible role of TNF-α and IFN-γ. Toxicology, 217(2-3): 206–12.

Kushwaha SKS, Rastogi A, Rai AK and Singh S, 2012. Novel drug delivery system for Anticancer Drug: A Review. *International Journal of Pharm Tech Research*, **4(2)** 542-553.

Mak P, Leung YK, Tang WY, Harwood C and Ho SM, 2006. Apigenin suppresses cancer cell growth through ER ß. *Neoplasia*, **8(11):** 896-904.

Manach C, Scalbert A and Morand C, 2004. Polyphenols: food sources and bioavailability. *American Journal of Clinical Nutrition*, 79: 727-747.

Maung TW, 2007. Berberine as a selective lung cancer agent. US20070298132.

Mukherjee R, Khattar D, Jaggi M, Singh AT, Kumar M and Bala H, 2004. Method for treating cancer using betulinic acid rich herbal extract. US20040116394.

Nijsen F, Rook D, Brandt C, Meijer R, Dullens H, Zonnenberg B, de Klerk J, van Rijik P, Hennink W and van het Schip F, 2001. Targeting of liver tumour in rats by selective delivery of holmium-166 loaded microspheres: a biodistribution study. *Eur J Nucl Med*, **28(6):** 743-749.

Olivi A, Ewend MG, Utsuki T, Tyler B, Domb AJ, Brat DJ, and Brem H, 1996. Interstitial delivery of carboplatin via biodegradable polymers is effective against experimental glioma in the rat. *Cancer Chemother Pharmacol*, **39:** 90-96.

Osterlind A, 1992. Epidemiology on malignant melanoma in Europe. *Acta Oncology*, 31 (8): 903-08.

Page TK, 2003. Herbal formulation. US6649185.

Pandey, Govind and Madhury S, 2006. Medicinal plants: better remedy for neoplasm. *Indian Drugs*, 43(11): 869-74.

Polterait O, 1997. Antioxidants and free-radical scavengers of natural origin. *Current Organic Chemistry*, **1:** 415-40.

Pouget C, Lauthier F, Simon A, Fagnere C, Basly J, Delage C and Chulia A, 2001. Flavonoids: structural requirements for antiproliferative activity on breast cancer cells. *Bioorganic and Medicinal Chemistry Letters*, **11(24):** 3095-97.

Qazi GN, taneja SC, Singh J, saxena AK, Sethi VK, Shah BA, Kapahi BK, Andotra SS, kumar A, Bhushan S, Malik F, Mondhe DM, Muthiah S, Verma M and Singh SK, 2009. Use of semisynthetic analogues of boswellic

acids for anticancer activity. US20090298938.

Rai N, Agrawal RC and Khan AS, 2011. Chemopreventive potential of *Centella asiatica* on B6F10 Melanoma Cell lines in experimental Mice. *Pharmacologyonline*, **1:** 748-758.

Saha P, Mazumder UK, Haldar PK, Naskar S, Kundu S, Bala A and Kar B, 2011. Anticancer activity of methanol extract of *Cucurbita maxima* against Ehrlich ascites carcinoma. *International Journal of Pharmaceutical Research Scholars*, **2(1):** 52-59.

Sarkar FH, Li Y, 2009. Harnessing the fruits of nature for the development of multi-targeted cancer therapeutics. *Cancer Treatment Review*, **35:** 597-607.

Saxena AK, Gupta BD, Kapahi BK, Muthiah S, Mondhe DM, Baleshwar N, Qazi GN, Kumar V nad Mathan G, 2006. Pharmaceutical composition useful for the treatment of hepatocellular carcinoma. US20060280817.

Shaban A, Mishra GM, Nautiyal R, Shrivastava S, Tripathi K, Chaudhary P and Verma S K, 2012. Invitro cytotoxicity of *Moringa oleifera* against different human cancer cell lines. *Asian Journal of Pharmaceutical and Clinical Research,* **5 (Supp 4)**: 271-272.

Shawi AA, Rasul A, Khan M, Iqbal F and Tonghui M, 2011. Eupatilin: A flavonoid compound is isolated from the Artimisia plant, induces apoptosis and G2/M phase cell cycle arrest in human melanoma A375 cells. *African Journal of Pharmacy and Pharmacology*, **5(5):** 582-588.

Singla AK, Garg A and Aggarwal D, 2002. Paclitaxel and its formulation. International Journal of Pharmaceutics, **235:** 179-192.

Svejda B, Moser VA, Sturm S, Hoger H, Ingolic E, Siegl V, Stuppner H and Pfragner R. 2010. Anticancer activity of novel plant extracts from *Trailiaedoxa gracilis* (W.W. Smith and Forrest) in Human Carcinoid KRJ-I Cells. *Anticancer Research Journal*, **30(1)**: 55-64.

Taylor JLS, Rabe T, Mc Graw L J, Jager A K and Staden J, 2001. Towards the Scientific validation of traditional medicinal plants. *Plant Growth Regulation*. **34:** 23-37.

Torchilin VP, 2001. Structure and design of polymeric surfactant-based drug delivery systems. *Journal of Controlled Release*, **73:** 137-172.

Tsang CM, Echo LPW, Di K, Cheng PY, Hau PM and Ching YP, 2009. Berberine inhibits Rho GTPases and cell migration at low doses but induces G2 arrest and apoptosis at high doses in human cancer cells. *International Journal of Molecular Medicine,* **24:** 131-138.

UNESCO (1998). FIT/504-RAF-48 Terminal Report: Promotion of Ethnobotany and the Sustainable use of Plant Resources in Africa, Paris, pp. 60.

Vishnupriya P, Radhika K, Prameela DY and Rao AS, 2011. Evaluation of anti-cancer activity of *Tridax procumbens* flower extracts PC3 cell lines. *PHARMANEST-An International Journal of Advances in Pharmaceutical Sciences*, **2(1):** 28-30.

Wang N, Feng Y, Lau PW, Tsang CM, Ching YP and Man K, 2010. F-actin reorganization and activation of Rho signalling pathway involved in the inhibitory effect of *Coptidis rhizoma* on hepatoma cell migration. *Integrated Cancer Therapy,* **9:** 354-364.

Wang N, Feng Y, Zhu M, Tsang CM, Man K, Tong Y and Tsao SW, 2010. Berberine induces autophagic cell

death and mitochondrial apoptosis in liver cancer cells: The cellular mechanism. *Journal of cell biochemistry*, **111(6):** 1426-1436.

Zhang S, Bao Y, Sun Y, Li K, Zou L, Ma J, Sun X, Shang H and Li J, 2010. Cyclin-dependent protein kinases inhibitor of *Scutellaria* flavonoid organic amine derivatives, synthesis and use thereof. US20100197619.

Ziech D, Anestopoulos I, Hanafi R, Voulgaridou GP and Franco R, 2012. Pleiotrophic effects of natural products in ROS-induced carcinogenesis. The role of plant-derived natural products in oral cancer chemoprevention. *Cancer Letters*, **327:** 16-25.