Borneol as Adjuvant Chemotherapy: A New Way for the Development of Novel Chemotherapeutic

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Abstract

Nature has generously open life-saving remedies to mankind by offering evolutionarily optimized drug like bimolecular in the form of several natural products. These marvelous gifts of nature have been serving as most suitable candidates against the treatment of multiple disorders and particularly for cancer (2⁰ leading cause of death, cancer) due to their pleiotropic mode of action on target molecules. Current review intends to provide an update on the bioactivities of such gifts from nature, natural borneol, which is the major bioactive constituents of traditionally used medicines. Borneol is a monoterpenoid, isolated from different medicinal plants and have strong potential to be used against multiple disorders such as bacterial and inflammatory infections. Recently it is investigated that borneol has a great potential of inhibiting the growth of multiple neoplasms such as hepatocellular carcinoma, neuroblastoma, glioma, esophageal squamous cell carcinoma, ovarian and lung cancer. Moreover, by regulating the BBB junctions it also increases the drug concentration in cancer cells, this shows that its combine use with already practiced therapeutics may increase the efficacy of these therapeutics against cancer cells. In this review we will summarize all the studies on anticancer activity of borneol, our primary goal will be to discuss the combined use of borneol with other clinically used drugs to improve their efficacy against human cancers.

Keywords: Borneol, Chemotherapy, Adjuvant therapy, curcumin and Doxorubicin borneol.

INTRODUCTION

The term “natural product” is usually used to refer those chemicals which are derived from nature (Nageen et al., 2018). The natural products contain possibly valuable bioactive agents for herbicides, pharmaceuticals, and insecticides industries. Till present time, more than 23,000 bioactive compounds have been reported since the penicillin discovery. Natural products are described as human health encouraging agents due to their high efficacy, low cost, and safety profiles (Newman et al., 2016). Different plants have already in use from a long time to cure numerous diseases. WHO claimed that 80% of the world population mainly depends upon plant-based medications for maintaining healthy lifestyle (Sen et al., 2015). Utilization of natural bioactive products have been used since 2600 BCE, when civilization of Mesopotamian used almost extract of 1000 plants to isolate various phytochemicals. Similar trend was manifested by Chinese civilization since 1100 BCE, where they used about 365 plant-based drugs (Mitin et al., 2016). In modern times, discovery of novel drugs from different natural sources involves the use of numerous phytochemicals, biological, molecular, and botanical techniques (Sen et al., 2015).

Research on different herbs and plants has been reported their high efficacy against multiple disorders. Studies have shown that bioactive molecules derived from multiple herbs and plants have antimicrobial (Hatzizeremia et al., 2006), anticancer (Wei et al., 2019), anti-inflammatory (Agus Chahyadi et al., 2012), skin whitening agents (Lee et al., 2006), antioxidant (also shows that versatile pharmacological activities of medicinal plants are mainly dependent upon their phytochemical components (Amira et al., 2018).
Cancer is a complex disease that has been described by unrestricted proliferation of cells caused due to mutation in several important genes that involve in encoding of multiple key proteins such as anti-apoptotic, tumor suppressors proteins as well as growth factors. Cancer is the 2nd leading cause of deaths both in developed and developing countries (Ashaq et al., 2021). Mainly chemotherapy has been used till date for the treatment of cancer which has restricted therapeutic success due to, toxicity, high expenses, and very quick development of resistance. Moreover, chemotherapeutic agents activate multiple other signaling pathways in parallel of suppressing the growth of cancer cells, such actions of chemotherapeutic drugs also limited their efficacy against different cancer cells (Mehmood et al., 2017). Cancer treatment by nature-based bioactive agents is now getting fame because they can improve the limitations of the chemotherapeutic agents used today (Muller et al., 1973).

Most of the pharmaceutical drugs are multitarget entities but bioactive compounds are multitargeted and can control proliferation of cells and cancer growth by modifying multiple signaling pathways (Muller et al., 1973). It is estimated that approximately 60% of clinically used anticancer drugs have been isolated from different natural sources including microorganisms, marine biota, and plants (Dall’Acqua et al., 2014). Phytochemicals acquired from fruits, herbs, vegetables, and different medicinal plants have shown promising effects in reducing the burden of cancer (Rabi et al., 2009). Secondary metabolites such as terpenoid, phenols, polyphenols flavonoids and isoprenoids isolated from several medicinal plants have been described for their possible anticancer activities (Niedzwiecki et al., 2016; Akinwumi). Moreover, bioactive agents have low side effects, easily available and cost effective that’s why use of biomedicines against multiple disorders has been increased day by day.

Borneol (C_{10}H_{16}O) is mainly obtained from a resin or dipterocarp and several medicinal plants as described in table 1 (Gao et al., 2013; Xie et al., 2016). Borneol is a monoterpenoid and bicyclic bioactive molecule as given in figure 1. It has been widely used in drug and food industries as a valuable medicinal material and flavorant respectively (Xie et al., 2016). Borneol have been used as an analgesic, antibacterial, and anti-inflammatory agent (Lai et al., 2020).

Furthermore, studies have shown that Borneol efficiently improved the availability of different less permeable therapeutics by improving permeability of cell membrane, regulating blood-brain barrier (BBB) and increasing the distribution of drugs in brain tissues (Cai et al., 2008; Duan et al., 2016). In addition to other medicinal values, it has been also reported that Borneol significantly increase the anticancer efficacy of various chemotherapeutic agents against human cancers (Su et al., 2016; Chen et al., 2014; Liu et al., 2018; Meng et al., 2018). In this review we will explore the anticancer mechanism of Borneol and discuss its multiple cellular targets in human cancers. Moreover, we will also discuss the combined use of Borneol with already used chemotherapeutics against different cancers.

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Table 1: Describes different medicinal that contain borneol in their different parts.

| Plants/Animal                  | Family    | Part of the plant | References       |
|-------------------------------|-----------|-------------------|------------------|
| Chrysanthemi Indicum          | Asteraceae| Flowers           | Deng et al., 2006|
| Amomum villosus               | Zingiberaceae | Not reported | Ye et al., 2008 |
| Cinnamomum camphora           | Lauraceae | Leaves            | Yang et al., 2018|
| Cinnamomum cassia,            | Lauraceae | Leaves            | Wang et al., 2009|
| Cinnamomum zeylanicum,        | Lauraceae | Leaves            | Wang et al., 2009|
| Cinnamomum tamala,            | Lauraceae | Leaves            | Wang et al., 2009|
| Cinnamomum burmannii,         | Lauraceae | Leaves            | Yang et al., 2020|
| Cinnamomum pauciflorum        | Lauraceae | Leaves            | Wang et al., 2009|
| Lavandula angustifolia        | Lamiaceae | Leaves            | Abroomand et al., 2011|
| Typus physiologions           |           | Leaves            | Zhang et al., 2010|
| Rosmarinus officinalis        | Lamiaceae | Leaves            | Okoh et al., 2010|
| Achillea millefolium          | Asteraceae| Flowers, Leaves   | Bocevska et al., 2007|
| Artemisia argyi               | Asteraceae| Inflorescences    | Weniqiang et al., 2006|
| Blumea balsamifera            | Asteraceae| Leaves            | Wang et al., 2014|
| Dryobalanops aromatica        | Dipterocarpaceae | Not reported | Le et al., 2016|
| Zingiber officinale           | Zingiberaceae | Rhizomes | Nishimura et al., 1995|
Main cellular targets of borneol include apoptosis, alleviated oxidative stress and sensitized the cancer cells to anticancer drugs (Hur et al., 2013; Su et al., 2018; Meng et al., 2017; Liu et al., 2014; Chen et al., 2018). Borneol reduced cell growth, increased cell cycle arrest, induced apoptosis, alleviated oxidative stress and sensitized the drug resistant cancer cells by modulating different signaling pathways such as p-Akt, p- ERK1/2 and p-JNK (Su et al., 2013; Hur et al., 2013; Chen et al., 2014; Chang et al., 2018). Main cellular targets of borneol are given in Table 2. Moreover, literature showed that there are diverse studies which explains the co treatment of borneol with different FDA approved anticancer drugs (Liu et al., 2018; Meng et al., 2018; Chang et al., 2018). Here in this review, we will further explain about the efficacies of borneol with different anticancer drugs and bioactive molecules against different cancers.

### Table 2: Different Molecular targets of Natural Borneol in multiple cancer cell lines

| Type of cancer | Cell lines | Molecular Targets | References |
|---------------|------------|-------------------|------------|
| Hepatocellular Carcinoma | HepG2 | p-Histone, p-p38, ROS, Caspase-3/8/9, Cl- PARP, Bad, Bax, t- Bid, p-p53, p-ATM, G2/M arrest, p-p53, p21, p-Histone | (Su et al., 2013) |
| | | TME65, FTH1, CTSB, Ca5b, PPI6C, BCKDHB, MRPL39, HNRNP, Fdps, AHCY, Fam185a, PDHA1, RCN3, RCN3, P4HA1, NDUFS1, ALDH1L2, G2/M arrest, p21, p-p53, p-ATM, ROS | |
| | | Ub-YFP, pre-G1 & G0/G1 arrest, p62 | |
| Neuroblastoma | SH-SY5Y | HO-1, Nrf2, Bcl-2, | (Hur et al., 2013) |
| | | ROS, Bax, | |

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| Cancer Type                          | Cells | Associated Proteins                                                                 | Treatment                                                                 |
|-------------------------------------|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Melanoma                            | A375  | sub-G1 arrest, Cl- PARP, p- JNK, ROS, p- ATM, p- Brcal, p-p53, Caspase-3/8/9,         | p-ERK, Akt                                                                |
|                                     |       |                                                                                      | (Chen et al., 2014)                                                       |
| Glioma                              | U251  | Caspase-3/8/9, p- ATM, ATR, p- p53, ROS, p- JNK, p- P38, p- ERK, Sub G1 arrest, p-    | Akt                                                                      |
|                                     |       | histone,                                                                              | (Cao et al., 2020)                                                       |
|                                     | U87   | ROS, p- ATM, p- ATR, p-p53, G2/M arrest, p- histone, p21, p- P38, p- ERK,             | Cyclin B, Cdc2, Akt                                                       |
|                                     |       |                                                                                      | Ki-67, CD34                                                              |
|                                     | U251  | Caspase-3/8/9, Bax, Bad, ROS, p- ATM, p- ATR, p- p53, p- histone H2A.X, p21            | MMP, Bcl-2, Bcl-XL                                                      |
|                                     |       |                                                                                      | (Liu et al., 2018)                                                       |
|                                     | U251  | Caspase-3, Bax,                                                                         | HIF-1 α, mTORC1, eIF4E, Bcl-2, p- eif4e                                  |
|                                     |       |                                                                                      | (Wang et al., 2020)                                                       |
| Esophageal Squamous cell Carcinoma  | TE-1  | Caspase-3,                                                                             | survivin , P- AKT                                                        |
|                                     | TE-13 |                                                                                      | (Meng et al., 2018)                                                       |
| Ovarian Cancer                      | A2780 | p- gp, MMP                                                                             |                                                                           |
|                                     | paclitaxel resistant A2780/PTX            |                                                                         | (Zou et al., 2017)                                                       |
| Lung Cancer                         | A549  | p- JNK, ROS, p- p53, TRPM8, Caspase-3/8/9, Cl- PARP, t- Bid, Bax, p- ATM, p- ATR,    | p- ERK, p- Akt, MMP, Bcl-2                                              |
|                                     |       | p- histone H2A.X, Sub G1, ROS, FADD, RIPK1                                              | (Lai et al., 2020)                                                       |
|                                     |       |                                                                                      |                                                                           |
|                                     |       |                                                                                      |                                                                           |
|                                     |       |                                                                                      |                                                                           |

**Borneol as an Adjuvant Therapy**

Mostly drugs used for cancer treatment are highly specific in their targets, but as cancer is caused by multiple mutations (Ashaq et al., 2021), thus it is usually observed that the cotreatment of more than one drugs in the treatment of cancer is more effective as compared to monotherapy. Recently it is reported that borneol (BRN) works along with different chemotherapeutic agents to boost the antineoplastic effect by different mechanisms (Chen et al., 2015; Cao et al., 2019). It is reported that BRN enhanced the anticancer effect of different clinically used anticancer drugs and bioactive molecules such as doxorubicin (DOX), curcumin (Cur), cisplatin and paclitaxel (Ptx) (as in table 3) by increasing the production of reactive oxygen species (ROS) that may induce cell cycle arrest, DNA damage (Cao et al., 2019) and activate p53 pathway (Chen et al., 2015), and enhancing apoptotic rate by regulating the expressions of multiple proapoptotic MAPK proteins and PI3K/Akt pathway in U251 cells (Cao et al., 2020; Yuan et al., 2020).

In addition to all this, BRN has been reported to easily cross the blood-brain barrier (BBBr), and some anticancer drugs, such as nimustine, arsenic trioxide, cisplatin, and methotrexate promoted its penetration through the BBBr (Xiao et al., 2009; Guo et al., 2008; Wang et al., 2020). Effect of cotreatment of BRN with different anticancer drugs and bioactive molecules is given in table 2. Further we will describe the cotreatment of BRN with different clinically practiced drugs and plant derived bioactive molecules.
| Cancer Type (Cell lines) | Natural Borneol (Concentration) | Drug (Concentration) | Mode of Action | Reference |
|--------------------------|---------------------------------|----------------------|---------------|-----------|
| Human Melanoma (A375)    | 40 mg/ml                         | Cur (10-40 μM)       | Natural broneol (NB) synergized the anticancer potential of Curcumin (Cur) in A375 cells | (Chen et al., 2014) |
| Human Glioma (U251 and U87) | (80 µg/ml)                       | Doxorubicin (DOX) (0.4 -0.8 μM) | NB synergized DOX-induced antineoplastic efficiency in glioma cells by increasing the uptake of DOX. | (Cao et al., 2019) |
| Human Glioma (U251 and U87) | NB (5-80 μg/ml)                  | Cisplatin (40 μg/ml) | NB synergistically increased cisplatin-induced cell death in human glioma. | (Cao et al., 2020) |
| Hepatocellular Carcinoma (HepG2) | NB (20 μg/ml)                    | BDCur (40 μM)        | NB enhanced the antiproliferative effect of BDCur by increasing uptake of BDCur via downregulation of ABCB1 expression. | (Chen et al., 2015 a) |
| Hepatocellular Carcinoma (HepG2) | NB (20 μg/ml)                    | Cur (20 μM)          | NB boosted the anticancer effect of Cur by increasing the cellular concentration of Cur through downregulating the expression of ABCB1. | (Chen et al., 2015 b) |
| Glioma (HBMEC, C6)       | NB (10 μg/mL)                    | Angiopep-2-modified, DOX-loaded PAMAM Dendrimer (20 μM/L) | NB synergized the antiglioma activity of DOX-loaded dendrimers by boosting its BBB penetration. | (Han et al., 2017) |
| Lung Cancer (A549)       | NB (40-160μg/mL)                 | DOX (0.25 μM)        | NB enhanced the anticancer activity of Doxorubicin through synergistic effects in A549 lung cancer cells | (Lai et al., 2020) |
| Human Glioma (U251)      | NB (80 μM)                       | Temozolomide (TMZ) (40 μM) | NB enhances TMZ-mediated antineoplastic efficiency against U251 through enhancing mitochondrial dysfunction and ROS-mediated DNA damage | (Liu et al., 2018) |
| Human Glioma (C6, BMEC cells) | DOX BO-PMs                      |                      | Increased cytotoxicity of Dox by increasing its transport efficiency across BBB and quick accumulation in brain tissues. | (Meng et al., 2019) |
| Esophageal squamous cell carcinoma (TE-1, TE-13) | NB (20-80 μg/mL) | Paclitaxel (PTX) (15 μM) | NB synergistically enhances the anticancer activity of Paclitaxel by increasing cellular accumulation of Paclitaxel in ESCC cells. | (Meng et al., 2018) |
| Hepatocellular carcinoma (HepG2) | NB (80 & 160 μg/μL)              | Selenocystine (20 & 40 μM) | NB effectively synergizes the Selenocystine-mediated cell death by enhancing cellular uptake of Selenocystine and activation of ROS-mediated DNA damage. | (Su et al., 2013) |
| Glioma (C6)              | BOR/PTX LANs (BOR: 1.0 μg/ml and PTX LANs: 50 μg/ml) |                      | NB in the form of BOR/PTX LANs sensitizes the PTX resistant cells by increasing its cellular uptake and accumulation of PTX inside the tumor tissue via inhibition of p-gp protein. | (Tang et al., 2015) |
| Glioblastoma (U87MG)     | NB (10 μg/ml)                    | CGKRK-PSNPs (200 μl) | NB enhances the cytotoxicity of CGKRK-PSNPs in U87-MG cells by increasing its transportation across BBB. | (Lv et al., 2020) |
| Lung cancer (A549)       | NBNPs (160-400 μM)               | Gefitinib (20-40 μM) | NBNPs synergistically potentiate the anticancer effect of Gefitinib by increasing cellular concentration of Gefitinib. | (Yuan et al., 2020) |
| Ovarian cancer (A2780/PTX cells) | PTX+NB co-delivery PEG-PAMAM NPs |                      | NB synergized the anticancer activity of PTX by increasing the cellular concentration of PTX in ovarian cells, via downregulation of p-gp protein. | (Zou et al., 2017) |

**Doxorubicin and Borneol**

DOX, an anthracyclene easily soluble in water, is the most efficient and broadly practiced chemotherapeutic mediator, which shows a wide range of cytotoxicity against different tumors (Chlebowski et al., 1979). Recently it has become a clear crystal fact...
that, DOX has severe harmful effects, such as dose-limiting myelosuppression and lethal cardiotoxicity (Carvalho et al., 2009). Moreover, the antineoplastic activity of DOX can be reduced by the MDR that is carried out by multiple drug efflux pumps (Wijdeven et al., 2016; Lipinska et al., 2017). Hence, lessening adverse effects, conquering chemo-resistance, and augmenting the antiproliferative activity remained the major hurdle for DOX-based treatment.

Nowadays, adjuvant therapy has become a promising method of searching novel chemo-sensitizers (Zhong et al., 2018; Cao et al., 2019). NB is a naturally occurring monoterpoid which has been reported as a potential chemosensitizer. It is reported that NB has a strong potential to increase the cytoxicity of DOX against different neoplasms by increasing cellular uptake and drug accumulation of DOX (Han et al., 2017; Cao et al., 2019; Meng et al., 2019). Meng et al., (2019) reported that natural borneol-modified nanomicelles loading doxorubicin (DOX BO-PMs) effectively increased the cellular uptake of DOX in the C6 and HBMEC cells through BBB by opening the tight intracellular junctions in the BBB, changing its conformation, enhancing the interactions of cell membrane, and accelerating the transport of nanomicelles.

Increase in cellular accumulation of DOX by NB also increases the anticancer effect of DOX in C6 via inhibition of cell growth in C6 cells. Moreover, it’s quite surprising that NB specifically acted on BBB not on tumor cells. In addition to increase the cellular accumulation of DOX, DOX BO-PMs also increased the antitumorigenic activity of DOX in liver cells and glioblastoma mouse model (Meng et al., 2019). Therefore, Angiopep-2 can be used for drug delivery into the brain and the glioma cells (Ji et al., 2019). Researcher shows that angiopep-2-PEG-PAMAM/DOX dendrimers modified with NB increased the anti-glioma activity of DOX by boosting BBB penetration of DOX-loaded dendrimers in C6 and HBMEC cells (Han et al., 2017). Another study conducted by Cao et al., (2019) demonstrated that NB enhanced the cellular uptake of DOX by increasing its BBB permeability (from 23.5% to 57.6%) in U251 cells. NB (20–160 μg/ml) alone did not reduce the cell growth in U251 cells but combined treatment of NB (80 μg/ml) with 0.4 or 0.8 μM DOX significantly increased the DOX-mediated growth inhibition of U251 cells. In addition, the decline of cell populations, cell shrinkage and cell rounding are also confirmed this conclusion.

Furthermore, NB also increased the growth inhibitory action of DOX by arresting cell cycle at G2/M phase via downregulation of Cyclin B1 and cdc2 (Cao et al., 2019). In A549 cells alone DOX (0.06 μM to 0.25 μM) showed a slight growth inhibitory effect but strong growth inhibition was observed in A549 cells pretreated with NB chased by low dose of DOX, with suppression ratio enhanced up to 40.26%. In A549 cells NB mainly increase the cytotoxic activity of DOX by increasing its cellular uptake and inhibiting the activity of P-glycoprotein (P-gp: one 9 of the major causes of DOX-resistance). NB boosted the DOX-induced cell death in A549 cells by increasing DOX-mediated apoptosis. NB enhanced the DOX-mediated activation of caspases cascade and increased apoptosis by upregulating both intrinsic and extrinsic apoptosis followed by PARP cleavage in A549 cells. Lai et al., (2020) also confirmed that NB and DOX have no cytotoxic effect on normal NCM-460 cells (colonic cells) which further confirmed the effective combined use of NB and DOX for cancer cells (Lai et al., 2020).

ROS plays crucial role in regulating cell proliferation, growth, migration, and death. Overproduction of ROS may cause DNA damage and regulate DNA damage-mediated different signaling transduction. NB increased the DOX-induced production of ROS, that ultimately augmented the DOX-mediated DNA damage as also evidenced by increased activation of phosphorylated ATR, p53, ATM, total p21 and histone H2A.X in U87 and A549 cells (Cao et al., 2019; Lai et al., 2020). Pretreatment of U87 cells with 5mM GSH significantly reduced the NB-DOX-induced DNA damage as reported by weak phosphorylation of ATR, p53, ATM, total p21, histone H2A.X and retrieved expressions of Cyclin B in U87 cells. These results disclosed that ROS as an influential upstream regulator aided to cotreatment-induced antineoplastic efficiency against glioma growth (Cao et al., 2019). In addition to it, Lai et al., (2020) demonstrated that DNA damage-mediated activation of p53 also contributed to the sensitizing impacts of NB on DOX in A549 cells. In A549 cells NB also synergistically enhanced the killing potential of DOX by increasing the mitochondrial dysfunction that was evidenced by lower membrane potential (∆Ψm), increase expression of Bax and tBid and decreased expression of Bel-2 (Lai et al., 2020).

PI3 K/AKT and MAPKs pathways have significant role in cell proliferation, survival, and death via phosphorylation of multiple substrates, thus inhibition of these pathways may reduce cell proliferation of different neoplasms. NB in cotreatment with DOX significantly cause the dysfunction of PI3 K/AKT and MAPKs pathways by dephosphorylating AKT (Ser473) and phosphorylating the ERK (Thr202) and p38 (Thr180) in U87 cells. Moreover, pretreatment of U87 cells with MAPKs and PI3K/AKT inhibitors may reduce the growth inhibitory effect of NB-DOX (Cao et al., 2019). In another study Lai et al., (2020) also reported that, in A549 cells NB synergize the DOX-induced apoptosis by inhibiting ERK and AKT activation while increasing the JNK and p38MAPK activation (Lai et al., 2020).
Besides in vitro studies NB also augmented DOX-mediated antineoplastic efficacy in vivo. Cao et al., (2019) showed that caudal vein administration of NB+DOX (20-40mg/kg NB+ 2mg/kg DOX) synergistically increased the anticancer effect of DOX in U251 cells bearing nude mice without significant loss of body weight in nude mice. Results of this in vivo study also showed that combined use of NB and DOX also arrested the cell cycle at G2/M phase and in vivo DNA damage as evidenced by phosphorylation of histone and inhibition of Cyclin B respectively. In addition to this immunohistochemical staining has demonstrated that combined treatment also eradicated expressions of CD34 and Ki-67, which are the key markers of angiogenesis and phosphorylation (Cao et al., 2019).

In another in vivo study NB+DOX have been administered both orally and intravenously in A549 cells bearing nude mice. Results of this study indicated that combined use of NB+DOX significantly reduced the tumor volume after 15 days of treatment in both orally and intravenously animal model but results clearly demonstrated that intravenously administration of NB+DOX showed more effective antitumor effect than oral administration. In addition, to all this concentration of DOX in tumor tissues was also high among intravenously administered group. Moreover, decreased expressions of Ki-67 and CD34 were also observed in tumor sections. Furthermore, in A559 cells NB synergize with DOX to accomplish potent antitumor efficacy through prompting intracellular Ca2+ mobilization by intermingling with TRPM8 (Lai et al., 2020).

**Selenocystine and Borneol**

Selenium (Se) has been found as an essential (trace) element of fundamental importance for both animals and humans. It has become a clear crystal fact that specific amount of Se can inhibit the growth of many neoplasms particularly in colon, lung, prostate, and liver cancers (Chen et al., 2009; Rayman et al., 2005). Studies have also inferred that Se can be clinically used in chemotherapeutic strategies (Bjorkhem-Bergman et al., 2005; Fan et al., 2009). However, Se presented a narrow margin between the toxic and beneficial effects. The effective concentration of Se as an antineoplastic agent, is too close to its toxic range, which significantly reduced its clinical application. Moreover, being a trace element, it may cause severe toxicity in normal cells when it’s taken in excess amount. Many studies have been clearly revealed that the toxic and beneficial effects of Se on human body were strongly correlated to its chemical forms and concentration (Rayman et al., 2005; Bjorkhem-Bergman et al., 2005; Fan et al., 2009). Selenocystine (SeC), a diselenide oxidative product of selenocysteine, has been reported to minimize the tobacco-derived nitrosamine-induced lung cancer in A/J mice (Li et al., 2007).

Moreover, SeC induced apoptosis in cancer cells by increasing the production of ROS (Chen et al., 2009), which subsequently increased the DNA damage-mediated expressions of p-p33 and lowered the expressions of ERK and Akt. Besides in vitro studies SeC also possessed in vivo anticancer actions by increasing the apoptosis in animal model (Chen et al., 2008). However, the low solubility of SeC and poor stability hampered its permeabilization across cell membrane and further development as an antitumor drug (Su et al., 2013). Therefore, its hypothesized that cotreatment of SeC with other biologically active molecules may increase its anticancer potential against various neoplasms. Su et al., (2013) suggested that NB can enhance the in vitro anticancer activity of SeC by increasing its cellular concentration in cancer cells. Results of Su et al., (2013) showed that pretreatment of HepG2 cells with NB (60 mg/mL and 160 mg/mL) significantly increased cellular uptake of SeC from 0.07 mg/107 cells (control) to 2.56 mg/107 cells, which was 1.6 times higher as compared to SeC alone. In addition, cotreatment of SeC (20 mM) and NB (60 mg/mL) noticeably increased the growth inhibition in HepG2 cells by inducing apoptosis which was evidenced by increased nuclear condensation, DNA fragmentation and increased expressions of caspase-3/8/9, caspase-3/7, and cleaved PARP in HepG2 cells. Furthermore, results of western blot described that cotreatment of HepG2 cells with SeC and NB increased the expressions of Bad, Bax, truncated Bid (tBid) and decreased expressions of Bcl-2, Bcl-XL and Mcl-1 (Su et al., 2013). tBid an activated form of Bid protein and member of BH3 domain-protein family, is well known due to its proapoptotic activity and build a link between the intrinsic and extrinsic apoptotic pathways. Moreover, activation of tBid causes its translocation from cytoplasm to mitochondrial membrane and led to oligomerization Bax and Bak, thereby increase the release of proteins from mitochondria to cytoplasm.

Synergistic apoptotic effect of SeC and NB in HepG2 cells was further evidenced by increased expressions of p-p38 MAPK and decreased expressions of p-ERK1/2 and p-Akt. Su et al., (2013) also suggested that SeC and NB potentially increased ROS production in HepG2 cells, surprisingly pretreatment of HepG2 cells with NAC significantly reduced the SeC and NB induced apoptosis in HepG2 cells, these results clearly concluded that ROS may act as upstream regulator SeC and NB induced apoptosis (Su et al., 2013).

**Curcumin and Borneol**

Curcumin (Cur), bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a biologically active constituent of *Curcuma longa*, which is extensively used in food industry as a coloring agent, spice, food preservative as well as major component of various traditional medicines. In last few years, pile of studies clearly reported that Cur can be potentially used as an antioxidant, antiproliferative, anti-inflammatory,
antiangiogenic, and anticancer agent. Different studies reported that Cur can inhibit the growth of multiple neoplasms such as hepatocellular carcinoma, thyroid cancer, colon cancer, breast cancer, bladder cancer, and ovarian cancer. Despite of its wide range bioactivities, its application is very limited because of its poor absorption, low bioavailability, and rapid metabolism. Several methods such as preparation of liposomes, nanoparticles, phospholipid complexes, micelles, and structural analogues of Cur have been used to enhance its cellular uptake and absorption rate. In addition to all this, recently it is proposed that combination of Cur with different drugs can also be used to increase the bioavailability of Cur which may increase its medicinal value. In recent decades it is reported that anticancer potential of Cur can be easily enhanced by its cotreatment with NB (Chen et al., 2014; Chen et al., 2015b).

Results of different studies have been reported that NB noticeably increased the cellular concentration of Cur in time-dependent manner, thus, pretreatment of A375 and HepG2 cells with NB (20-40 mg/ml) significantly decreased the cell viability in Cur-treated A375 and HepG2 from 70% to 54.20% (Chen et al., 2014; Chen et al., 2015b). Combined use of NB and Cur can potentially induce apoptosis in cancer cells by regulating different pathways. Chen et al., (2014) revealed that combined use of Cur and NB induced a significant nuclear condensation and DNA fragmentation in A375 cells which were not found in the cells treated with Cur and NB alone. Literature showed that cotreatment of Cur and NB noticeably augmented the activation of caspase-3/8/9 which ultimately increased the expressions of cleaved PARP in A375 cells. Activation of caspase-3/8/9 in A375 cells on the cotreatment of Cur and NB clearly demonstrated that both Cur and NB can induce apoptosis in cancer cells by activating both intrinsic as well as extrinsic apoptotic pathways.

Pretreatment of A375 cells followed by Cur treatment significantly increased the production of ROS which resulted in the increased phosphorylation of p-p53, p-ATM, p-Brc1 and p-JNK while decreased the expressions of p-AKT and ERK1/2 in a dose-dependent manner (Chen et al., 2014). Studies also have suggested that the mitogen-activated protein kinases (MAPKs) signaling pathway plays a vital role in the action of different chemotherapeutic treatments (Chen et al., 2008) and regulating progression of cell cycle and cell death or growth. Jun amino terminal kinases (JNK), extracellular regulated protein kinases (ERK) and p38MAPK pathways are the three most valuable pathways in MAPKs pathway. p38MAPK and JNK are mostly activated by stress and enhanced apoptosis, whereas ERK, could avert cell apoptosis by reducing the activation of caspases (Bold et al., 2002). The Akt pathway also played a crucial role in cell proliferation and cell death by transferring different signals to inhibit apoptosis (Abrams et al., 2010; Cho et al., 2013).

Above discussed results clearly demonstrated that Cur/NB caused the upregulation of ROS, that plays a major role in the activation and inhibition of JNK and AKT and ERK respectively to increase the Cur/NB induced cytotoxicity and apoptosis in A375 cells. Different studies revealed that proteasome subunit alpha type-5 (PSMA5), nucleophosmin (NPM) and heterogeneous nuclear ribonucleoproteins C1/C2 (hnRNPC1/C2) proteins involved in DNA repair, RNA splicing, apoptosis, and cell cycle arrest (Chen et al., 2015 b). PSMA5 is a subunit of 20S proteasome, a proteolytic enzyme found in the nucleus and cytoplasm of eukaryotic cells (Han et al., 2004). Previous studies reported that inhibition of the PSMA5 can cause cell cycle arrest and apoptosis in cancer cells (Xu et al., 2008; Liu et al., 2004; Clarke, 2002). hnRNPC1/C2, a member of hnRNP family, is a nuclear pre-mRNA binding factor that mainly regulate processing of pre-mRNA, apoptosis, and cell cycle. NPM is a vital player in regulation of cell cycle, response of DNA-damage and an important modulator of p53 by regulating the expressions of Mdm2 (Chen et al., 2015b). In a recent research it is documented that NB/Cur can induce cell cycle arrest by modulating PSMA5, NPM and hnRNP C1/C2 which ultimately leads to apoptosis in cancer cells. Results of a recent report demonstrated that NB/Cur exposure to HepG2 cells markedly induced cell cycle arrest at G2/M phase by upregulating the expressions of p21, p-p53, p-ATM, ROS and downregulating the expressions of cyclin B1, cdc2, PSMA5, NPM, Mdm2 and hnRNP C1/C2 (Chen et al., 2015b). Interestingly, pretreatment of HepG2 cells with NAC significantly reduced the NB/Cur-induced G2/M phase arrest from 33.1% (when exposed only to NB/Cur) to 13.9% (when pretreated with NAC), which was evidenced by downregulation of p21, p-p53, and histone. These results clearly depicted that ROS can be an upstream target of G2/M phase arrest in HepG2 cells, thus plays a crucial role in NB/Cur-induced apoptosis in HepG2 cells (Chan et al., 2015b).

**Bisdemethoxycurcumin (BDCur) and Natural Borneol**

Turmeric’s major constituents include curcumin (Cur), bisdemethoxycurcumin (BDCur) and demethoxycurcumin (DCur). Many studies have been suggested the beneficial impacts of curcuminoids, particularly Cur. Studies have been proven that Cur possesses anti-inflammatory, antioxidant, anticancer and anti-angiogenic activities (Yang et al., 2012; Shi et al., 2006). In parallel to Cur, only a few studies have been reported about the beneficial effects of BDCur, a dimethoxy derivative of Cur (Chen et al., 2015a). Recent studies have suggested that BDCur inhibited the cell proliferation and survival of different neoplasms including breast cancer, colon cancer, leukemia, and glioma cells. In addition, BDCur suppressed cancer...
invasion and metastasis by suppressing MMPs and uPA in HT1080 cells (Chen et al., 2015a; Ramezani et al., 2017). However, its beneficial effects are extremely limited due to its low absorption which might be due to its poor water solubility. Therefore, anticancer activities of BDCur can be enhanced by increasing its cellular uptake. Recently Chen et al. (2015b) has been reported that antineoplastic action of BDCur can be increased by its cotreatment with NB. Results of MTT assay showed that BDCur (10, 20, 40, 80 μM) alone can induce cytotoxicity in HepG2 cells and LO2 cells in a dose-dependent manner, but cell viability was quite high in LO2 cells as compared to HepG2 cells. NB (10, 20, 40, 80 μg/ml) alone did not inhibit the cell growth in HepG2 and LO2 cells. Further studies suggested that NB increased the anticancer potential of BDCur by increasing its cellular concentration in HepG2 cells in a time-dependent manner via inhibition of ABCB1 (Chen et al., 2015a). Growth inhibitory mechanism of BDCur and NB suggested that combined use of both BDCur and NB significantly induced cell cycle arrest in HepG2 cells at G2/M phase, which is evidenced by high level of ROS, increased expression of p21, p-ATM, p-histone (Ser 139 site) and decreased expression of p-MDM2, Cdc2 and Cyclin B1 in HepG2 cells. Chen et al., (2015a) also described that pretreatment of HepG2 cells with NAC (inhibitor of ROS generation) significantly reduced the growth inhibitory effect of NB/BDCur which clearly shows the ROS as upstream target of cell cycle arrest in HepG2 cells (Chen et al., 2015a).

CONCLUSION

Borneol is a bioactive molecule that belongs to terpenoid, a group of secondary metabolites of plants. It has been reported that borneol has wide medicinal value to be used against different disorders. In our review we clearly discussed about the anticancer effect of borneol, borneol has potential to reduce the growth of multiple neoplasms by regulating different signaling pathways. It induces apoptosis in different cancer cells by increasing the expressions of proapoptotic proteins, lowering the antiapoptotic proteins and activating both intrinsic and extrinsic pathways of apoptosis. It also suppressed the cell growth by modulating different pathways including MAPKs and PI3K/Akt pathway. Moreover in vivo studies shows that it has very high cytotoxicity for cancer cells while very low toxic effect for normal cells. In combined use with other clinically used drugs borneol significantly increased their concentration in cancer cells and thus improve their efficacy against cancer cells in vitro. In addition to all this borneol also sensitize the drug resistance cancer cells by inhibiting the expressions of p-gp. All these studies clearly describe the potential role of borneol against different neoplasms, however further preclinical and clinical trials are needed to ensure its development as a novel therapeutic for cancer.

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