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Current development in integrative therapy of traditional Chinese medicine for cancer treatment: A mini-review

Po-Hsuan Su^a, Chen-Jei Tai^{a, b, *}^a Department of Traditional Chinese Medicine, Taipei Medical University Hospital, Taipei, 11031, Taiwan^b Department of OB/GYN, School of Medicine, College of Medicine, Taipei Medical University, Taipei, 11031, Taiwan

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ABSTRACT

Cancer is a major public health problem worldwide, and there has been a sustained rise in its incidence in both developing and developed countries. Although there are currently numerous effective therapeutic options for cancer, they sometimes exhibit resistance and obvious side effects. Traditional Chinese medicine (TCM) currently plays a major role in cancer therapy by downregulating the growth of cancer cells through various pathways and by relieving side effects. Studies in cultured human malignant cell lines have demonstrated that *Solanum nigrum* can control cancer cell proliferation and cancer progression by inducing autophagic and apoptotic cell death. Case–control studies have indicated that TCM can relieve the side effects of cancer therapy. This review provides brief insights into the anticancer effects of TCM, the side effects relieved by TCM, and the role of TCM doctors in cancer treatment.

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1. Introduction

Cancer results from the abnormal proliferation of cells that fail to undergo apoptosis.¹ This leads to the accumulation of morphologically abnormal cells and causes tumor formation.² Therefore, one of the cancer treatment targets is to induce cell death or apoptosis.² However, conventional anticancer treatments may sometimes have therapeutic limitations caused by the resistance to anticancer drugs or the development of side effects such as neutropenia, severe fatigue, hepatitis, nausea, and vomiting, because of which patients are forced to stop or postpone treatment courses.^{3–5}

Traditional Chinese medicine (TCM) has been increasingly used

in anticancer treatment; it reinforces healthy qi and eliminates pathogenic factors.⁶ Modern pharmacological and clinical studies have demonstrated that TCM induces autophagic cell death, prevents resistance to anticancer drugs, and relieves severe side effects during conventional anticancer treatments.^{7,8}

In this mini-review article, we reveal that TCM plays a major role in cancer therapy through 3 actions: first, providing basic research evidence supporting that the aqueous extract of *Solanum nigrum* (AESN) controls cancer cell proliferation and cancer progression; second, proving the effectiveness of TCM for relieving side effects during chemotherapy and target therapy; and third, establishing a TCM doctor consulting and referral system for patients with cancer during their admission to a hospital or an outpatient department.

2. Anticancer effects and mechanisms of AESN in basic research

Solanum nigrum (SN) (龍葵 *lóng kuí*), commonly known as Makoi or black nightshade, is a medicinal herb widely used as an elemental ingredient in TCM formulas; it contains many steroidal glycosides, steroidal alkaloids, steroidal oligoglycosides, including solamargine, solasonine, solavilline, solasdamine, solanine, flavonoids, steroidal saponins and glycoprotein. Many polyphenolic

Abbreviations: TCM, traditional Chinese medicine; AESN, aqueous extract of *Solanum nigrum*; SN, *Solanum nigrum*; IC₅₀, half maximal inhibitory concentration; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; ROS, reactive oxygen species; EMT, epithelial–mesenchymal transition; SQDBT, Shi Quan Da Bu Tang; AST, aspartate transaminase; ALT, alanine transaminase; EGFR, epidermal growth factor receptor.

* Corresponding author. Department of Traditional Chinese Medicine, Taipei Medical University Hospital, Taipei, 11031, Taiwan.

E-mail address: chenjtai@tmu.edu.tw (C.-J. Tai).

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compounds such as gallic acid, protocatechuic acid, catechin, caffeic acid, epicatechin, rutin, and naringenin, which possess strong antioxidant and anticancer activity. The steroidal alkaloids and glycoproteins are exhibiting anti-tumor activity. It also exhibits antiproliferative, hepatoprotective, antioxidant, and anti-inflammatory activities. In the clinical practice of TCM, a therapeutic agent is typically prepared by mixing the aqueous extracts of various medicinal herbs according to various formulas.⁹ Some common aqueous extracts of medicinal herbs present in TCM formulas used for cancer treatment exhibit anticancer efficacy in numerous human cancer cells *in vitro*.¹⁰ In recent years, the *in vitro* anticancer effects of SN extracts have been observed in various cancers, such as leukemia, prostate, liver, breast, lung, stomach, colon, and bladder cancers.^{10–12} In this section, we provide brief insights into the anticancer pathway of AESN and its benefit as an adjuvant to chemotherapy for endometrial adenocarcinoma cells, colorectal carcinoma cells, hepatocellular carcinoma cells, ovarian carcinoma cells, and breast cancer cells from our studies.

2.1. Effect of AESN on endometrial adenocarcinoma cells

Tai et al.¹³ confirmed 3 outcomes.

2.1.1. Cytotoxicity of AESN in human endometrial adenocarcinoma HEC1A, HEC1B, and KLE cells

In the study by Tai et al.,¹³ human endometrial adenocarcinoma HEC1A, HEC1B, and KLE cells were treated with AESN. After incubation, based on the half maximal inhibitory concentration (IC_{50}) value, AESN treatment was more effective for HEC1A ($IC_{50} = 0.56$ mg/mL for AESN) and HEC1B cells ($IC_{50} = 0.38$ mg/mL for AESN) than for KLE cells ($IC_{50} = 1.6$ mg/mL for AESN).

2.1.2. Determination of cell-death-related protein markers in AESN-treated endometrial carcinoma cells

Among 3 principal cell death markers (PARP, caspase-3, and LC-3 A/B), caspase-3 is a cell death marker of caspase-dependent apoptosis, whereas PARP is a cell marker activated during both apoptosis and necrosis. In addition, the accumulation of LC-3 A/B-II indicates the activation of autophagic cell death. In all 3 cell lines treated with AESN, no cleavage of PARP and caspase-3 was observed, whereas the accumulation of LC-3 A/B-II was statistically significant. These results suggested that AESN mainly activated autophagic rather than apoptotic and necrotic cell death in the 3 tested human endometrial adenocarcinoma cell lines.

2.1.3. Synergistic effects of AESN on docetaxel-treated HEC1A and HEC1B cells

According to the IC_{50} value determined through the cell viability study, docetaxel and AESN cotreatment exerted a combination effect in HEC1A and HEC1B cells, whereas KLE cells were not only less sensitive to AESN but also resistant to docetaxel treatment. These results suggested that cotreatment with AESN further enhanced the cell cytotoxicity of docetaxel in HEC1A and HEC1B cells.

In conclusion, AESN treatment was effective in suppressing endometrial cancer cells through the autophagic pathway and enhanced the cytotoxicity of docetaxel in human endometrial cancer cells.

2.2. Effects of AESN on colorectal carcinoma cells

Tai et al.¹⁴ demonstrated the following outcomes:

2.2.1. AESN cytotoxicity and autophagy induction in HT-29 and DLD-1 human colorectal carcinoma cells

In the study by Tai et al.,¹⁴ human colorectal carcinoma HT-29

and DLD-1 cells were treated with AESN. After incubation, based on the IC_{50} value of AESN and according to the results of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, the cytotoxicity of AESN was caused by the disruption of the mitochondrial metabolism. The IC_{50} values were 0.541 and 0.948 mg/mL in DLD-1 and HT-29 cells, respectively. Under microscopic inspection, lipid-like droplets were observed in AESN-treated DLD-1 and HT-29 cells. This morphological feature suggested that AESN-treated cells were in the autophagic process, which might be related to AESN-induced cytotoxicity. In addition, the accumulation of the protein marker LC3 A/B II indicated that the cell death mechanism of AESN-induced cytotoxicity involved autophagy.

2.2.2. Combined effects of AESN and cisplatin, doxorubicin, docetaxel, and 5-FU

Tumor cells were treated with serial doses of 4 chemotherapeutic drugs, namely cisplatin, doxorubicin, docetaxel, and 5-FU, alone or in combination with AESN. AESN presented enhanced cytotoxicity in combination with all 4 chemotherapeutic drugs. Analysis revealed the synergistic effects of AESN combined with each chemotherapeutic drug. The IC_{50} value of each chemotherapeutic drug significantly decreased when combined with AESN in comparison with each chemotherapeutic drug alone. These *in vitro* results suggested that AESN could enhance the tumor suppression effects of cisplatin, doxorubicin, docetaxel, and 5-FU in human colorectal carcinoma cells when combined with these chemotherapeutic drugs.

2.2.3. Activation of LC3 A/B and caspase-3 in AESN- and chemotherapeutic drug-treated cancer cells

The apoptotic protein marker cleaved caspase-3 and the autophagic protein marker LC3 A/B II were subsequently determined in the total protein extracts of the cells. The results indicated that all tested drugs activated caspase-3 and produced cleaved caspase-3 in DLD-1 cells, but not in HT-29 cells, whereas AESN increased LC3 A/B II levels in both cell lines. This result suggested that AESN enhanced cytotoxicity when combined with chemotherapeutic drugs and induced LC3 A/B II accumulation in colorectal carcinoma cells.

In conclusion, AESN induced tumor cell death in HT-29 and DLD-1 cells in a caspase-3-independent manner through the activation of autophagy, demonstrated tumor suppression efficacy against DLD-1 and HT-29 human colorectal carcinoma cells, and further enhanced tumor cell death when combined with tested chemotherapeutic drugs in human colorectal carcinoma cells.

2.3. Effects of AESN on hepatocellular carcinoma cells

Wang et al.¹⁵ revealed 2 major results as follows:

2.3.1. Cytotoxicity of AESN alone and combined with chemotherapeutic drugs in Hep3B and HepJ5 cells

In the study by Wang et al.,¹⁵ human hepatocellular carcinoma Hep3B and HepJ5 cells were treated with AESN. Based on the IC_{50} value of AESN and according to the results of the MTT assay, AESN inhibited cell growth and demonstrated cytotoxicity in Hep3B and HepJ5 cells. Compared with cisplatin or doxorubicin alone, the IC_{50} values for cisplatin and doxorubicin combined with AESN were reduced by 40% and 30%, respectively. These results suggested that the AESN treatment potentiated cisplatin- and doxorubicin-induced cytotoxicity in both Hep3B ($IC_{50} = 0.96$ mg/mL for AESN) and HepJ5 cells ($IC_{50} = 0.97$ mg/mL for AESN).

2.3.2. Activation of programmed-cell-death-related proteins in AESN- and chemotherapeutic drug-treated cancer cells

AESN combined with cisplatin or doxorubicin activated LC-3 A/B and caspase-7 in the 2 hepatocellular carcinoma cell lines. The results suggested that in both Hep3B and HepJ5 cells, AESN induced LC-3 A/B II accumulation in all treatment groups. The cleavage of caspase-7 was enhanced by AESN cotreatment in cisplatin-treated Hep3B and HepJ5 cells and in doxorubicin-treated HepJ5 cells, but not in doxorubicin-treated Hep3B cells.

In conclusion, AESN cotreatment potentiated cisplatin- and doxorubicin-induced cytotoxicity in human hepatocellular carcinoma cells. This AESN-potentiated cytotoxicity occurred through the accumulation of LC-3 A/B II and the cleavage of caspase-7 for activating apoptosis and autophagic cell death in human hepatocellular carcinoma cells. AESN can be integrated in chemotherapy with cisplatin and doxorubicin to improve tumor suppression efficiency in human hepatocellular carcinoma cells.

2.4. Effects of AESN on ovarian carcinoma cells

The anticancer effects of AESN were reported by Wang et al.¹⁶ from 3 aspects.

2.4.1. Cytotoxicity of AESN in ovarian cancer cells

In the study by Wang et al.,¹⁶ human ovarian cancer ES-2, SKOV-3, and OVCAR-3 cells were treated with AESN. According to the results of the MTT assay and based on IC_{50} values, OVCAR-3 cells were more resistant ($IC_{50} > 2$ mg/mL for AESN) to AESN treatment than ES-2 and SKOV-3 cells ($IC_{50} = 1.052$ and 1.779 mg/mL for AESN, respectively). AESN-treated ES-2 and SKOV-3 cells exhibited obvious morphological changes and apoptotic features, such as cell shrinkage as well as the formation of lipid-like droplets, which is considered a feature of autophagy. Compared with the test human ovarian cancer cells, normal hOG cells did not exhibit any growth inhibition after AESN treatment. This indicated that AESN-induced cell growth inhibition is likely specific to ovarian cancer cells and does not occur in normal cells.

Furthermore, AESN treatment induced LC-3 A/B II accumulation in ES-2, SKOV-3, and OVCAR-3 cells and caspase-3 activation in SKOV-3 cells.

2.4.2. Combinational effects of AESN with cisplatin, doxorubicin, and docetaxel on human ovarian cancer cells

ES-2, SKOV-3, and OVCAR-3 cells were cultured with AESN and cisplatin, doxorubicin, or docetaxel, and cell viability was analyzed using the MTT assay. IC_{50} value analysis indicated that AESN enhanced the cytotoxicity of cisplatin, doxorubicin, and docetaxel in both ES-2 and SKOV-3 cells but enhanced the cytotoxicity of only cisplatin in OVCAR-3 cells.

To further identify the combinatorial effects of AESN with the tested chemotherapeutic drugs, we used a combination index analyzed using the Calcsyn software program. Combination index values < 1 indicated synergistic effects. All combination index values for ES-2 cells exposed to $2\text{--}50$ μM doxorubicin and 0.5 mg/mL AESN were < 1 , suggesting that this combination produces synergistic effects.

Overall, both IC_{50} values and combination index values suggested that AESN treatment enhanced the tumor suppression efficiency of cisplatin, doxorubicin, and docetaxel in human ovarian cancer cells.

2.4.3. Treatment with AESN activated caspase-3 cleavage in SKOV-3 cells

SKOV-3 cells were treated with AESN alone or in combination with chemotherapeutic drugs. Caspase-3 was cleaved in SKOV-

3 cells treated with both AESN alone and in combination with drugs. The semiquantification results indicated that AESN further enhanced cleaved caspase-3 accumulation in SKOV-3 cells when combined with the 3 drugs. These results suggested that AESN enhanced the cytotoxicity of the selected drugs by promoting caspase-3 cleavage in ovarian cancer cells.

In conclusion, this study demonstrated the tumor suppression efficacy of AESN and the combinatorial cytotoxic effects of AESN with cisplatin, doxorubicin, and docetaxel in human ovarian cancer ES-2, SKOV-3, and OVCAR-3 cells. These findings suggest that AESN is an antitumor agent that can be integrated with current chemotherapeutic drugs to treat ovarian cancer.

2.5. Effects of AESN on breast cancer cells

Lai et al.¹⁷ examined the anticancer effects of AESN mediated through various pathways as follows:

2.5.1. Suppression of breast cancer MCF-7 cells through AESN treatment

In the study by Lai et al.,¹⁷ breast cancer MCH-7 cells were treated with AESN. After AESN treatment, MCF-7 cells were arrested in the G2/M phase of the cell cycle. This result suggested that AESN could limit the proliferation of MCF-7 and result in cell death.

2.5.2. AESN treatment induced apoptosis in breast cancer MCF-7 cells

Through propidium iodide–Annexin V double staining, AESN clearly resulted in apoptosis in MCF-7 breast cancer cells.

2.5.3. Mechanism and mitochondrial morphology of apoptotic MCF-7 breast cancer cells

Through fluorescent staining, AESN markedly increased caspase-3 levels, and according to dichlorodihydrofluorescein diacetate staining, AESN clearly increased the reactive oxygen species (ROS) level in breast cancer MCF-7 cells. In terms of mitochondrial morphology, mitochondria fission was induced and visualized after AESN treatment. This result indicated that AESN may affect mitochondrial activity and regulate proliferation and apoptosis in breast cancer MCF-7 cells.

2.5.4. Influence of chemotherapy resistance and inhibition of metastasis by AESN

The epithelial–mesenchymal transition (EMT) results in invasive cells entering the blood stream. During EMT, a decrease was found in E-cadherin, occludins, claudins, and desmoplakin, as well as an elevation of vimentin, N-cadherin, fibronectin, and α -smooth muscle actin. In this study, we noted that AESN could attenuate N-cadherin, vimentin, and ZEB1 levels in breast cancer MCF-7 cells and could elevate the level of E-cadherin. This result indicated that AESN could reverse the EMT process for inhibiting metastasis and sensitizing cancer cells to chemotherapeutic agents.

In conclusion, through the suppression of EMT and apoptosis, AESN demonstrated significant cytotoxicity in human breast cancer cells. Furthermore, it enhanced mitochondrial fission, thus attenuating mitochondrial function in human breast cancer cells (Fig. 1).

3. Role of TCM in relieving the side effects of chemotherapy and target therapy

3.1. Hematotoxicity

Most patients with breast cancer require chemotherapy for relapse prevention. They often encounter various complications during or after chemotherapy, such as hematotoxicity.

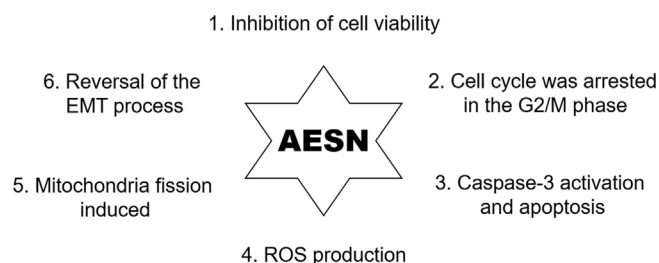


Fig. 1. Six main effects of AESN in breast cancer cell. ROS: Reactive Oxygen Species; EMT: Epithelial–Mesenchymal Transition.

Hematotoxicity has been reported to interfere with the completion of chemotherapy and to cause fatigue and weakness among patients. A tumor marker is a biomarker present in blood, urine, or body tissues that can be elevated by the presence of one or more types of cancer. In oncology, tumor markers indicate the presence of cancer. The tumor markers CEA and CA153 are associated with breast cancer.

A case–control study conducted by Huang et al.¹⁸ revealed that Shi Quan Da Bu Tang (SQDBT) (十全大補湯) is effective in alleviating hematotoxicity among patients with breast carcinoma receiving chemotherapy without affecting the presentation of the tumor markers CEA and CA153 (which indicate the presence of breast cancer).

In the aforementioned study, a total of 80 patients with breast carcinoma who received chemotherapy were identified. After excluding patients with WBC counts of $\geq 4000/\mu\text{L}$ and those who did not follow the usual 3-week cycle, 13 patients with SQDBT treatment comprised the case group, and 66 patients without SQDBT treatment comprised the comparison group. Complete blood count tests were conducted before the first chemotherapy was initiated, after completing the first chemotherapy, and 1 week after chemotherapy. The tumor markers CEA and CA153 were assessed every 3 months.

The results indicated that patients who received concomitant SQDBT treatment with chemotherapy exhibited significantly increased WBC, neutrophil counts, and Hb levels after chemotherapy compared with those in the comparison group. The tumor markers CEA and CA153 did not differ in patients who received concomitant SQDBT treatment with chemotherapy when compared with those in the comparison group.

3.2. Hepatotoxicity

Chemotherapeutic drugs that can damage the liver cells of recipients are classified as having potential hepatotoxicity. Chemotherapeutic drugs that are not classified as having hepatotoxicity may still induce poor liver function among patients because of considerable cell death resulting from chemotherapy.

A case–control study conducted by Liu et al.¹⁹ reported that using TCM could protect liver function by lowering serum aspartate transaminase (AST) and alanine transaminase (ALT) levels during chemotherapy.

In the aforementioned study, a total of 89 patients with cancer were identified; 37 patients received TCM treatment combined with chemotherapy, whereas 52 patients received chemotherapy only. The TCM medication used during chemotherapy included Xiao Chai Hu Tang (小柴胡湯), Huang Lian Jie Du Tang (黃連解毒湯), or Yin Chen Wu Ling San (茵陳五苓散) based on patient conditions evaluated by TCM doctors. The liver function test data (including AST and ALT levels) were collected 1 week before chemotherapy, during chemotherapy, and 2 weeks after chemotherapy.

The mean AST level did not differ significantly between case and control groups 1 week before and 2 weeks after chemotherapy. However, the case group had significantly lower mean AST levels during chemotherapy (mean AST levels of 26.55 declined to 24.12 versus mean AST levels of 24.76 increased to 29.20, $P = .01$). Mean ALT levels did not differ significantly between the case and control groups at all 3 time points. Nonetheless, the case group had lower mean ALT levels during chemotherapy, with borderline significance (mean ALT levels of 24.17 declined to 22.60 versus mean ALT levels of 22.70 increased to 26.33, $P = .08$). These results indicated that using TCM with chemotherapy may protect the liver during chemotherapy.

3.3. Paronychia

Patients with lung adenocarcinoma sometimes have common activating epidermal growth factor receptor (EGFR) mutations, more precisely deletions in exon 19 and L858R substitution mutations in exon 21. Therefore, targeting EGFR has become a crucial treatment strategy. Afatinib is a target therapeutic drug widely used to treat patients with mutant activating EGFR-dependent lung adenocarcinoma. However, it has various adverse side effects including diarrhea (95.2% of patients), rash or acne (89.1%), stomatitis or mucositis (72.1%), paronychia (56.8%), dry skin (29.3%), decreased appetite (20.5%), pruritus (18.8%), nausea (17.9%), fatigue (17.5%), vomiting (17.0%), epistaxis (13.1%), and cheilitis (12.2%).²⁰ Numerous people interrupt their therapies because of the serious adverse side effects. Therefore, reducing the adverse side effects will greatly improve patients' outcomes.

A case report published by Yang et al.²¹ revealed that TCM can cure paronychia induced by afatinib.

A female patient diagnosed with lung adenocarcinoma exhibited symptoms of paronychia with pain and tissue fluid exudation on both hands and the left foot after treatment with afatinib for a month. After receiving TCM medication, namely Jen Ren Hwo Minq Saan (真人活命散), Ban Zhi Lian (半枝蓮), and Bai Hua She She Cao (白花蛇舌草), for 4 months, the paronychia was completely cured.

4. Role of TCM doctors in the hospital system

TCM therapy has gradually played a crucial role in cancer therapy. From previous studies, TCM can not only be effective in suppressing cancer cells through the autophagic pathway but also enhance the cytotoxicity of chemotherapeutic drugs. In addition, it can relieve the various side effects of chemotherapy and target therapy. However, in Taiwan, even in the same hospital, a low number of patients with cancer receive both medical therapy and TCM therapy. Sometimes, this is because doctors from certain departments do not really understand the therapy provided by doctors from other departments, or the consulting system is not familiar to them. Most of the time, patients with cancer have to seek a solution themselves, and this will cause a delay in early diagnosis and treatment, cause them to receive unnecessary treatment, and increase the mortality rate. For this reason, establishing a consulting system between TCM doctors and Western medicine doctors is key to ensure complete and continuous treatment, and it would have great benefits for inpatients and outpatients. In Taipei Medical University Hospital, we established a similar consulting system. Medical doctors can consult and refer patients to TCM doctors in the same system. Once the consultation system is initiated, a text message will be sent to TCM doctors immediately. This function can enable TCM doctors to get acquainted with the medical record of the patient as soon as possible. After consultation with the TCM doctor, the patient and/or the family can bring the prescription to the cashier first and then

leave the prescription in the TCM pharmacy. TCM medication will be prepared by the TCM pharmacist and sent to the ward every day. Ward nurses will be responsible for delivering the medication to the patients, as ordered. TCM doctors will provide the prescription details and other related information in the medical record in the consultation system, and Western medicine doctors can access the therapy process, TCM diagnosis, and TCM prescription. Through this consultation system, patients with cancer will receive both Western medicine and TCM care, which will increase therapeutic efficiency. Moreover, through constant communication, medical progression will be promoted. It is the optimal approach for cancer treatment. Evidently, mutual trust is pivotal to establish long-term cooperation relationships in integrative therapy.

Conclusion

TCM plays a central and invaluable role during cancer therapy. Our review reveals that integrative therapy of TCM with modern chemotherapy or targeted therapy not only alleviates the side effects of cancer therapy in patients with cancer but also provides clinicians with more trustable data to improve treatment protocols.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jtcme.2019.07.001>.

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