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Research Article

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Theoretical Study on the complex of Calcium with Estrone: potential of Calcium as an Anti- Estrogen compound

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ABSTRACT

Breast cancer is the most common cancer and cause of cancer death among women around the world. The inhibitory effect of calcium in cell proliferation and incidence of breast cancer has been identified in some studies, although the exact of its mechanism is not clear very well. To further study the potential inhibitory effects of calcium in breast cancer, we used computational methods, the Becke three-parameter Lee-Yang-Parr (B3LYP). The results indicated that Calcium (Ca^{2+}), estrone (E_1) and Calcium – estrone complex, all after optimization, had the positive frequency and negative energies. The amount of the Gibbs free energy change (ΔGa) for Calcium absorption reaction on estrone was negative that represents spontaneous calcium absorption process on estrone. Therefore, it is possible that calcium reduce the cell proliferation and carcinogenesis by estrogen through producing a stable complex with estrone, changing estrone conformation and suppressing conversion of estrone to estradiol.

Key Words: Breast cancer, calcium, estrogen, B3LYP

INTRODUCTION

Breast cancer is the most common diagnosed cancer and major cause of cancer death among women. Breast cancer is responsible for about 23% of all cancer cases and 14% of deaths due to cancer [1]. Increased incidence of mammary neoplasia has been reported during the past few decades which led to the development of new anti-cancer drugs, drug combinations and new methods of chemotherapy [2]. Because of magnitude of the problem, considerable study has been devoted to reveal of the etiology of breast cancer.

Calcium is an important intracellular second messenger that there are some reports on its importance role in carcinogenesis development due to participate in cell proliferation, differentiation, apoptosis and cell signaling [3,4]. In experimental models of cancer it has been reported high intake of calcium can suppress hyperproliferation of mammary gland epithelial cell induced by high- fat diet and DMBA-induced breast cancer [4]. Several studies have been shown that serum calcium levels inversely associate with breast cancer risk among premenopausal women [5]. In conversely, other studies have been reported a positive association between serum calcium and breast cancer in premenopausal women [3]. Furthermore, it is clear that long-term exposure to estrogen either endogenous or

exogenous have a vital role in the development and progression of breast cancer [6,7], the precise molecular mechanisms by which estrogens can affect mammary tumor formation is not clear very well [8,9].

Density functional theory (DFT) method is common quantum computation method that energy and other molecular properties in ground state are accessible by applying electron probability density in ground state uniquely. B3LYP method is the most common function including local and nonlocal terms [10].

In this study, in order to optimization of calcium, estrogen and absorption process was used from B3LYP method and polarizing and influential basis set of 6-311++G**. Because of use from this basic set to optimize estrone, exist elements of oxygen with high electron density and hydrogen with high polarization because add polarization functions are essential for systems in which there is hydrogen. In addition, in species that the electron density usually is distributed to outside of molecule such as anions and molecules with nonbonding electron pairs and excited state are used mentioned influence functions [11].

Therefore, in present study we evaluate the process of calcium absorption on estrone to propose the new pathway in the potential of calcium in inhibiting of cell proliferation and breast cancer.

EXPERIMENTAL SECTION

In the entire process was used Hyperchem, Gaussviews 05 and Gaussian 09 software. All of calculations were performed by Gaussian 09 Windows that is very powerful program so that the rate of analysis increased 4 times rather than Gaussian 03.

At first, each of the compounds (calcium and estrone) was drawn by using Hyperchem software and then input file for calculations in Gaussian was made and computations for optimization and doing frequency in the gaseous environment was carried out by B3LYP method and 6-311++G** basis set. Finally, these compounds came together in Gaussviews and absorption process was done through relative keywords.

RESULTS AND DISCUSSION

As shown in Figure 1, Ca is able to alter the estrone conformation by binding to oxygen and carbon atoms from cyclopentane ring side.

The amounts of first frequency, energy, absorption energy (ΔEa) and ΔGa are shown in table 1.

The results showed that Ca, estrone and Ca - estrone complex, all show positive frequencies after optimization and with the energies -424761/18, -533288/95 and -958483/11 Kcal/mol, respectively. These values represent the absorption energy of -426/71 Kcal/mol. Also negative amount of ΔGa for reaction of Ca absorption on estrone that is equal to -424/82 Kcal/mol indicates the spontaneous absorption process of Ca on estrone.

Table 1. The amounts of first frequency and energy for calcium, estrone and calcium- estrone complex and absorption energy (ΔEa) and ΔGa for Ca on estrone.

Particulars	Ca	E_1	Ca- E_1 complex
First frequency[a]	-0.0008	43.5796	47.7443
Energy[b]	-424761.18	-533288.95	-958483.11
ΔEa[b]	—	—	-426.71
ΔGa[b]	—	—	-424.82
[a]Frequencies values was expressed as cm-1. *[b]Energy, ΔEa and ΔGa values was expressed as Kcal/mol.*			

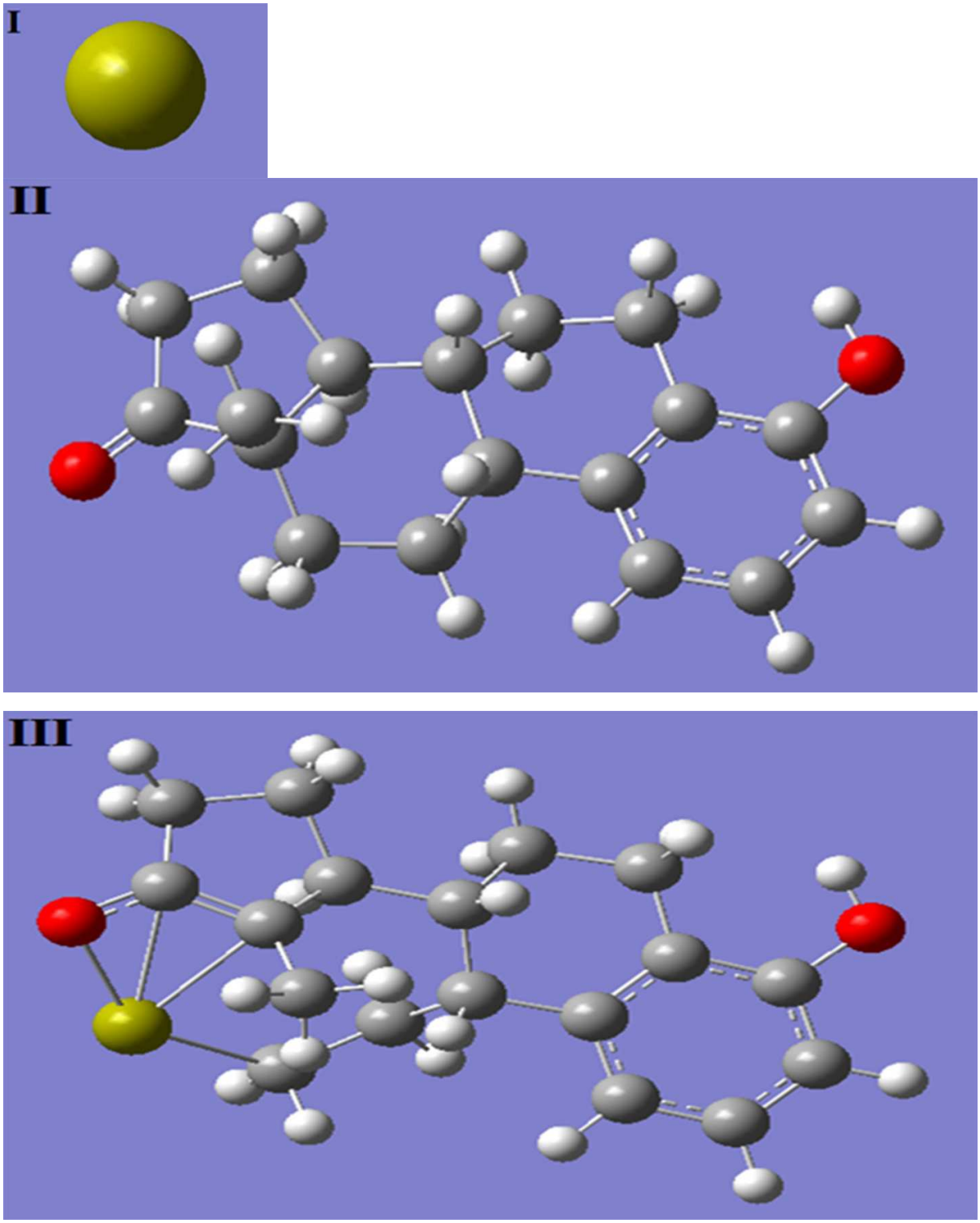


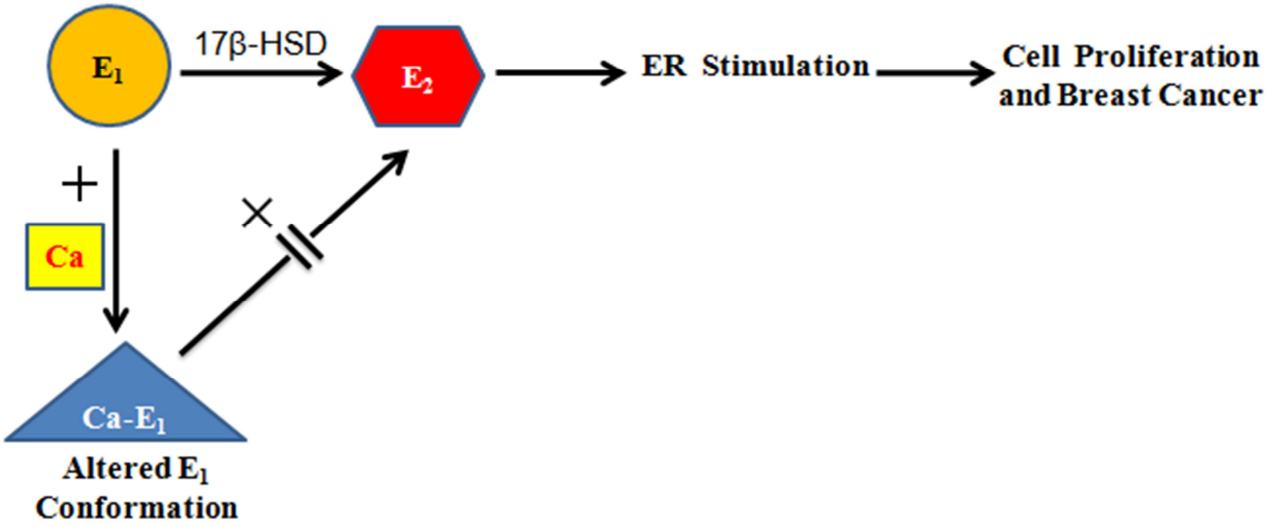
Fig. 1. I: structure of calcium, II: structure of E1 estrogen (estrone), III: structure of calcium - estrone complex, calcium bound to oxygen at carbonyl group and some carbon of estrone. (Yellow: Ca^{2+}, Red: Oxygen, White: Hydrogen and Gray: Carbon atom)

It has been reported that calcium reduces cell proliferation and induces differentiation of mammary cells in experimental works [4]. High intake of calcium has been shown to inhibit high-fat diet-induced epithelial

hyperproliferation of the mammary gland and mammary carcinogenesis induced by 7, 12-dimethylbenz (*a*) anthracene in the animal models [12, 13]. Clinically, it has been reported that calcium-rich diet intake in women is associated with a lower risk of breast cancer [14]. The main mechanism of the inhibitory effect of calcium in tumor genesis is not understand very well but some mechanisms such as participation in regulating cell proliferation, differentiation, apoptosis cell signaling have been suggested [13, 15, 16]. Furthermore, some evidence is available that calcium exerts its ant carcinogenic activity, at least partially, by vitamin D. For example, calcium is one of the key mediators of apoptosis induced by vitamin D compounds in breast cancer cells [17]. The results of present study show that calcium is able to bind to estrone and change it conformation. According to energy of this reaction the complex is stable very well. These finding guide us to propose a new way in the anti-cancer effect of calcium. Nowadays, there are many studies regarding association between risks of breast cancer with persistently elevated blood levels of estrogen. Approximately 70% of breast cancers are positive estrogen receptor (ER+). Estrogen induces progression of cell proliferation and breast cancer through the ER [14].

It is important to notice that estrone convert to estradiol by 17-β-hydroxysteroid dehydrogenase (17β-HSD) [6] and subsequently estradiol stimulates cell proliferation and carcinogenesis by binding to its receptor [6, 9].

The complex of calcium with estrone could restrain its conversion to estradiol. Therefore, because of reduced level of estradiol, stimulation of estrogen receptors and cell proliferation may decrease [6, 9].



CONCLUSION

The results of the present study propose that calcium produce a stable complex with estrone and reduce its free level. This complex, with changing the conformation of estrone, may inhibit the conversion of estrone to estradiol and subsequently decrease stimulation of ERs and cell proliferation.

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REFERENCES

[1] A Jemal; F Bray; MM Center; J Ferlay; E Ward; D Forman. *CA Cancer J Clin*, **2011**, 61 (2), 69-90.
[2] X Wang; S Yuan; J Wang; P Lin; G Liu; Y Lu; J Zhang; W Wang; Y Wei. *Toxicol Appl Pharm*, **2006**, 215 (2), 168-78.
[3] M Almquist; A-G Bondeson; L Bondeson; J Malm; J Manjer. *Int J Cancer*, **2010**, 127 (9), 2159-68.
[4] Y Cui; TE Rohan. *Cancer Epidem Biomar*, **2006**, 15 (8), 1427-37.
[5] BL Sprague; HG Skinner; A Trentham-Dietz; KE Lee; Klein BEK; R Klein. *Ann Epidemiol*, **2010**, 20 (1), 82-5.
[6] M Clemons; P Goss. *N engl J med*, **2001**, 344 (4), 276-85.

[7] A Lupulescu. *Exp Clin Endocr Diab*, **1993**, 101 (4), 204-14.
[8] W Yue; J-P Wang; Y Li; P Fan; G Liu; N Zhang; M Conaway; H Wang; KS Korach; W Bocchinfuso. *Int J Cancer*, **2010**, 127 (8), 1748-57.
[9] W Yue; JD Yager; J-P Wang; ER Jupe; RJ Santen. *Steroids*, **2013**, 78, 161–70.
[10] F Jensen. Introduction to computational chemistry, 2nd Edition, Wiley. com, **2007**.
[11] AE Frisch; JB Foresman. Exploring Chemistry with Electronic Structure Methods, 2nd Edition, Pittsburgh PA, Gaussian Inc, **1996**; Part 2, 302.
[12] EA Jacobson; KA James; HL Newmark; KK Carroll. *Cancer Res*, **1989**, 49, 6300 – 3.
[13] L Xue; M Lipkin; H Newmark; J Wang. *J Natl Cancer Inst*, **1999**, 91, 176 – 81.
[14] G Liu; X Hu; S Chakrabarty. *Cell Calcium*, **2009**, 45 (3), 216-225.
[15] CM McGrath; HD Soule. *In Vitro*, **1984**, 20, 652 – 62.
[16] J Russo; IH Russo. *Radiat Res*, **2001**, 155, 151 – 4.
[17] IS Mathiasen; IN Sergeev; L Bastholm; F Elling; AW Norman; M Jaattela. *J Biol Chem*, **2002**, 277, 30738 – 45.