Phytomedicine 23 (2016) 763–769

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.com/locate/phymed

Pause menopause with *Rhodiola rosea*, a natural selective estrogen receptor modulator

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ARTICLE INFO

Article history:
Received 28 October 2015
Revised 16 November 2015
Accepted 17 November 2015

Keywords:
Menopause
Selective estrogen receptor modulator
Rhodiola rosea
Cognitive function
Cardiovascular

ABSTRACT

Background: Menopausal women are challenged by the adverse effects of estrogen loss on energy, mood, cognitive function, and memory. These stresses are compounded by increased risks for cardiovascular disease, osteoporosis, and cancer. Known to have neuroprotective, cardio-protective, anti-oxidative and anti-carcinogenic effects, *Rhodiola rosea* extracts have also been shown to improve energy, mood, cognitive function and memory.

Purpose: We propose that *R. rosea* be investigated for use as a potential selective estrogen receptor modulator (SERM) in the prevention and treatment of menopause-related fatigue, stress, depression, cognitive decline, memory impairment, cardiovascular disease, osteoporosis and cancer.

Method: This paper briefly reviews the relationship between estrogen decline and menopause-related health risks, the molecular mechanisms underlying estrogenic effects on health, and the evidence indicating beneficial effects of *R. rosea* extracts on these mechanisms and health risks. Mechanisms include non-genomic and genomic effects, for example: activation of intra-cellular signal transduction pathways by binding to estrogen receptors, ERα-mediated activation of endothelial nitric oxide synthase with increased nitric oxide release; and anti-inflammatory effects, counteracting TNFα by inhibiting nuclear factor-Kappa-B (NF-$_K$B) and protection of osteoblasts from hydrogen peroxide. A clinical case illustrating treatment of a menopausal woman with *R. rosea* is presented. Risks, benefits, gaps in knowledge, and future directions are discussed.

Conclusion: Numerous lines of evidence indicate that *R. rosea* should be investigated as a potential selective estrogen receptor modulator (SERM) to prevent, delay or mitigate menopause-related cognitive, psychological, cardiovascular and osteoporotic conditions.

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Introduction and background

Menopause-related illnesses constitute a major public health concern. In countries where women's life expectancy exceeds 80 years, the average age of menopause (defined as the absence of menstrual cycle for 12 months) is 51. An inter-continental review estimated that women spend one third of their lives in menopause regardless of ethnicity or socio-economic factors (Makara-Studzińska, Kryś-Noszczyk, Jakiel, 2014). Menopause is often accompanied by declining energy, mood, cognitive function, and memory. In addition, menopausal women are at increased risks for cardiovascular diseases, dementia, osteoporosis, and cancer. It has been estimated that about half of women over the age of 50 will experience menopause-related symptoms that will cause somewhat or fairly difficult problems at work; about 5% will have severe difficulties (Kopenhager and Guidozzi, 2015).

Hormone Replacement Therapy (HRT), once thought to be the panacea for menopause, has fallen out of favor since findings from the Women's Health Initiative (WHI) indicated that: estrogen plus progestin does not provide cardioprotection and might increase the risk of coronary heart disease; estrogen plus progestin did not prevent mild cognitive impairment and increased the risk for dementia in postmenopausal women aged 65 and older (Manson et al., 2003; Shumaker et al., 2003). Although estrogen plus progestin increased bone mineral density (BMD) and decreased the risk of fractures, these benefits were not considered to outweigh the other possible

Abbreviations: ACE, angiotensin-1 converting enzyme; AD, Alzheimer's Disease; BMD, bone mineral density; AMT, adenosine monophosphate; ATP, adenosine triphosphate; eNOS, endothelial nitric oxide synthase; GABA, gamma-aminobutyric acid; NF-$_K$B, nuclear factor-Kappa-B; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; ER, estrogen receptor; EDV, endothelial-dependent vasodilation; MAPK, mitogen-activated protein kinase; OVX, ovariectomized; ROS, reactive oxygen species; SERM, selective estrogen receptor modulator; TNFα, Tumor necrosis factor-alpha.

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http://dx.doi.org/10.1016/j.phymed.2015.11.013
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increased health risks for breast cancer and venous thrombosis (Cauley et al., 2003). More recent interpretations of the WHI data on HRT distinguish between early menopause, as a time of less risk and greater benefit, *versus* later menopause (after 10 years), as a time of greater risk and less benefit (Chlebowski and Anderson, 2015; Roehm, 2015). Furthermore, the WHI Study found that in women 65 years of age and older and 15 or more years past the onset of menopause, HRT with conjugated equine estrogens (Premarin) did not improve cognitive function and slightly increased the risk of dementia (Luine, 2008). Studies of 17β-estradiol given during or shortly after the onset of menopause showed improvements in verbal memory, working memory, and visuospatial function with a comparatively lower risk of dementia (Frick, 2010).

Since the introduction of Premarin 75 years ago, no new treatments have been approved as HRT for menopause-related cognitive or cardiovascular symptoms. Selective estrogen receptor modulators (SERMS) are estrogen receptor ligands that exert estrogen agonistic or antagonistic activity in a tissue-specific manner. Starting in the 1990's, the development of SERMS has been directed towards preventing osteoporosis (agonists in bone) and reducing cancer risks (antagonists in breast tissue). Examples of SERMS include, tamoxifen for treatment of estrogen receptor (ER) positive breast cancer, raloxifene for postmenopausal osteoporosis, and bazedoxifene (BZA) to prevent osteoporosis while blocking estrogenic stimulation in breast and uterus. BZA combined with conjugated estrogens, is a new tissue-selective estrogen complex (TSEC) (Xu et al., 2015). Side effects of SERMS include fatigue, hot flushes, leg cramps, vaginal discharge, and mood swings. These prescription SERMS also increase the risk of arterial and venous thrombosis, pulmonary embolism and retinal vein thrombosis. Many women are reluctant to try synthetic SERMS, while others discontinue use after a few years. The quest continues for an ideal selective estrogen receptor modulator (SERM), the Holy Grail of menopausal medicine. The ideal SERM would exert agonistic effects on estrogen receptors (ERs) in bone, vascular and brain tissues, while simultaneously causing anti-estrogenic or no estrogenic effects in healthy breast, endometrial or ovarian tissue.

In deciding whether to initiate HRT, patients and physicians must weigh the risks, benefits, personal and family history, and other individual complicating factors. Many women choose to endure the discomforts of menopause rather than expose themselves to the risks associated with HRT. Women are placing greater importance on maintaining their physical and cognitive health, in part due to cultural changes in their expectations regarding their abilities to continue working, caring for family members, and functioning at higher levels later in life. These aspirations are reflected in the adage, "Seventy is the new fifty." Women are changing their lifestyles, exercising more, improving their diets, and hoping that healthy choices will mitigate the changes and the risks associated with menopause, even in the absence of definitive studies.

The search for effective alternatives to HRT is gaining momentum. Adaptogenic herbs contain numerous constituents that can act on estrogen receptors, intra-cellular signaling, genomic regulation, and inter-cellular transmission involved in supporting the brain functions that become impaired with estrogen decline and aging (Panossian et al., 2013, 2014; Panossian and Wikman, 2010). Certain physiological mechanisms whereby estrogen decline leads to common health problems experienced by menopausal women can be modulated by adaptogenic herbs, particularly *Rhodiola rosea*. Therefore, a review of the impact of R. rosea, estrogens, and estradiol, on neuroprotection, stress resistance, anxiety, depression, cardiovascular protection, osteoprotection, and cancer is in order. Data from *in vitro, in vivo* and clinical trials as well as case examples contribute to the growing evidence that supports the proposal that *R. rosea* be investigated as a potential SERM for the treatment of menopause-related symptoms.

Rhodiola rosea and salidrosides

Animal and human studies of *Rhodiola rosea* indicate that it can improve many of the neuropsychological symptoms experienced by menopausal women, including fatigue, anxiety, depression, cognitive dysfunction, memory decline, reduced executive functions, and stress intolerance (Bystritsky et al., 2008; Darbinyan et al., 2007; Gerbarg et al., 2015; Panossian, 2013; Panossian and Wagner, 2011; Shevtsov et al., 2003). Salidroside [2-(4-hydroxyphenyl)ethyl-β-D-glucopyranoside], a phenylpropanoid glycoside, is one of the bioactive constituents in *R. rosea* root extracts. Evidence indicates that *R. rosea* and salidroside may protect endothelial and cardiac function, reduce the risk of cancer, and cause fewer adverse effects compared with synthetic SERMS (Brown et al., 2009; Ciumaşu-Rîmbu et al., 2012; Xing et al., 2015; Zhang et al., 2012) . *In vitro* and *in vivo* studies of *R. rosea* extracts are extensive. Although the methodologies of some older studies of *R. rosea* extract have been criticized, the risk benefit ratio is considered to be favorable (European Medicine Agency, 2012).

Neuroprotection

Effects of estrogen on cognitive functions

Estrogen loss can exacerbate the effects of aging on cognitive functions, particularly learning, memory and executive functions. Estradiol enters the cell nucleus where it may bind to estrogen receptor alpha (ERα) or estrogen receptor beta (ERβ). The bound complexes function as nuclear transcription factors which bind to estrogen response elements, stimulating gene transcription and consequent increased production of cellular proteins that can enhance cognitive functions by increasing neural transmission, spinogenesis and synaptogenesis, for example, in the prefrontal cortex and hippocampus (Hara et al., 2015). These actions enhance memory formation, consolidation, storage and retrieval. Estradiol can initiate intracellular signal transduction pathways via ERs. In addition to genomic effects, through activation of ERα and ERβ, rapid nongenomic effects are mediated through membrane-bound ERα, ERβ, and membrane glucocorticoid protein coupled estrogen receptor 1 (GPER1) (Hara et al., 2015). These estrogen receptors are found in synapses in the hippocampus and prefrontal cortex. Estrogens synthesized locally in the brain can rapidly modulate cognitive and other neuronal functions (Luine, 2014).

Cholinergic and serotonergic systems function as biological mediators of hormonal effects on the brain (Comasco et al., 2014). Animal and human trials show that chronic administration of estradiol upregulates neuronal systems (including cholinergic, monoaminergic, gamma aminobutyric acid [GABA]-ergic, and glutaminergic) which enhance cognition, memory and emotion regulation (Levine, 2011).

Menopausal changes in reproductive hormone levels have been linked to an increased incidence of Alzheimer's Disease (AD) in women (Blair et al., 2015). The concept of a "critical window" between the onset of menopause and 10 years post-menopause has been used to explain why HRT may have beneficial effects such as reduced AD risk if given during early menopause, but no benefit and possibly adverse effects when given during later menopause (after 10 years) (Daniel et al., 2015). Studies of this "critical window" have produced mixed results. Oxidative stress and inflammatory cytokines contribute to progression of neuronal dysfunction associated with menopause.

Effects of rhodiola rosea and salidrosides on cognitive functions

Numerous *in vitro* and animal studies demonstrate neuroprotection by salidrosides. Clinical studies of *R. rosea* have shown improvement in cognitive functions and physical performance, especially

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