Adaptogens in chemobrain (part IV): adaptogenic plants prevent the chemotherapeutics-induced imbalance of redox homeostasis by modulation of expression of genes encoding Nrf2-mediated signaling proteins and antioxidant, metabolizing, detoxifying enzymes in neuroglia cells

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Background: We recently demonstrated that adaptogenic plant extracts prevent cytostatic drug-induced changes in transcriptome-wide mRNA microarray profiles of isolated neuroglial cells associated with neuronal function and cognitive impairment in cancer chemotherapy. The aim of the present study was to assess the effects of *Andrographis paniculate* (AP), *Eleutherococcus senticosus* (ES), *Rhodiola rosea* (RR), and *Schisandra chinensis* (SC) extracts and their combinations on fixed combination 5-fluorouracil, epirubicin, and cyclophosphamide (FEC)-induced transcriptome changes associated with nuclear factor erythroid 2-related factor-2 (Nrf2) signaling pathways in neuroglia cell culture.

Methods: Gene expression profiling was performed by transcriptome-wide mRNA microarray in human T98G neuroglia cells after treatment with adaptogens. Interactive pathway downstream analysis was performed with datasets of significantly up- or downregulated genes and predicted effects on cellular function and disease were identified by Ingenuity Pathway Analysis (IPA) software.

Results: FEC significantly deregulated 23 genes of the Nrf2 signaling pathways. Co-incubation with adaptogens induces the upregulation of heme oxygenase 1 gene expression and genes encoding Kelch-like ECH-associated protein (KEAP1) transcription factor and nuclear transcription factors MAF bZIP transcription factor F and MAF bZIP transcription factor G. Adaptogens prevent FEC-induced downregulation of genes PIK3R2 and *RALA* encoding Nrf2 upstream signaling proteins PI3K and Ras as well, as genes *NQO1*, *GSR*, *GCLC* encoding the expression of cytoplasmatic antioxidant and enzymes glutathione-disulfide reductase, NAD(P)H quinone dehydrogenase 1, and glutamate-cysteine ligase catalytic subunit.

Conclusions: The results of our study suggest that the beneficial effects of adaptogens on impaired neuronal and cognitive function are due to mitigating oxidative stress-induced cellular damage by multitarget regulation of redox homeostasis via the regulation of gene expression, activating KEAP1-Nrf2 signaling pathway proteins, and modulating antioxidant, metabolizing, and detoxifying enzymes.

Keywords: Oxidative stress; nuclear factor erythroid 2-related factor-2 (Nrf2); adaptogens; neurotoxicity; network pharmacology

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Introduction

Several plants widely used in traditional Chinese medicine (TCM), Ayurveda and other traditional medicinal systems, such as Panax ginseng Meyer root, Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. root (ES), Rhodiola rosea L. rhizome and root (RR), Andrographis paniculata L. Nees herb (AP), and Schisandra chinensis (Turcz.) Bail. (berry) (SC), are known for their pleiotropic effects, which are considered to be associated with the adaptogenic activity; that is, an ability to increase adaptability (presumably “xiehuo” in TCM), resilience, and survival of organisms in stress- and aging-related disorders (1-5). This could be due to increasing the “state of non-specific resistance” (6-8), which is negatively associated with the state of increased susceptibility to stressors—“shanghuo” or “re-qi” in TCM—resulting in disease progression due to threatened homeostasis (yin-yang balance) (9,10).

The neuroprotective, hepatoprotective, cardioprotective, antioxidant, immunomodulatory, antiviral, stress-protective, antifatigue, hypoglycemic, antidepressant, chemopreventive, and antitoxic effects of various adaptogenic preparations have been shown in many isolated cells and in experimental animal models (11-35).

The cytoprotective effect of andrographolide (AND; an active compound of AP), AP, ES, AP-ES combination, and ES-RR-SC combination on the chemotherapy-induced deregulation of gene expression in neuroglia cell culture has been recently demonstrated (36-38). These studies suggest that adaptogens might be useful for preventing and mitigating the toxic effect of chemotherapy in cancer (e.g., in “chemobrain”) (39), but also for reducing oxidative stress-induced cellular damage and detoxification in many inflammatory conditions, including low-grade chronic inflammation (“inflammaging”) in aging (40). Oxidative stress is increasing in aging-related disorders, including atherosclerosis, angiogenesis, and neurodegeneration (40,41). Oxidative stress-induced redox signaling results in cellular response and the activation of defense mechanisms, including the induction of antioxidant and detoxifying genes, including superoxide dismutase (SOD), glutathione S-transferase (GST), NAD(P)H quinone oxidoreductase-1 (NQO1), and heme oxygenase 1 (HO-1). Therefore, the activation of Nrf2 translocation or the upregulation of gene expression resulting in the activation of the Nrf2 signaling pathway is the key mechanism of cellular defense response associated with the antioxidant and detoxifying effects of medicinal plants (43-46), and particularly of adaptogenic plants, such as AP, RR, SC, and ES (47-71). However, their effect on the expression of genes encoding antioxidant enzymes, phase II and III metabolizing enzymes, and transports, as well on upstream transcription factors, has not been investigated. Therefore, the aim of the present study was to assess the effects of AND, AP, ES, AP-ES combination, and ES-RR-SC combination on chemotherapy [fixed combination 5-fluorouracil, epirubicin, and cyclophosphamide (FEC)]-induced gene expression related to Nrf2 signaling pathways in neuroglia T98G cell culture.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/lcm-20-24).

Methods

All materials and methods used in the present study have been described in detail in our previously published studies (36-38). The present study is a part of the same study; however, the results have not been published until now. Therefore, only short description of herbal extracts, mRNA microarray hybridization and ingenuity pathway analysis (IPA) is provided below.

Herbal extracts

Pharmaceutical-grade extracts were manufactured in accordance with the ICHQ7A and European Medical Agency guidelines for good agricultural and collection practice and good manufacturing practice of active pharmaceutical ingredients. Working samples used in the experiments were prepared by diluting dimethylsulfoxide (DMSO) solutions of the extracts with appropriate volumes of phosphate-buffered saline to obtain the same final
The concentrations of active markers in the incubation media.

The concentrations of the extracts and their active constituents were well-matched in all test samples; that is, the final concentration of AND was the same (2 μm, 700 μg/mL) in all test samples containing AND, and corresponded to the concentration of AND in human blood after the oral administration of a therapeutic dose (60 mg) of herbal (Table 1) (71). Similarly, eleuthero side E concentrations were calculated based on the results of HPLC analyses of its content in genuine extracts and AP-ES, ES-RR-SC combinations. The concentrations of genuine extracts were calculated using AE specifications to ensure that they corresponded to therapeutically effective doses (35).

Table 1 The concentration of drugs used to treat T98G neuroglial cells in microarray experiments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AND</td>
<td>0.7 (=2 µm)</td>
</tr>
<tr>
<td>AP</td>
<td>30.0 (AND =2 µm)</td>
</tr>
<tr>
<td>AP-ES</td>
<td>32.7 (AND =2 µm)</td>
</tr>
<tr>
<td>ES</td>
<td>2.7</td>
</tr>
<tr>
<td>ES-RR-SC</td>
<td>176</td>
</tr>
<tr>
<td>FEC</td>
<td>5-FU: 50; epirubicin: 0.5; 4-HC: 2</td>
</tr>
<tr>
<td>FEC + AND</td>
<td>5-FU: 50; epirubicin: 0.5; 4-HC: 2; AND: 0.7 (=2 µm)</td>
</tr>
<tr>
<td>FEC + AP</td>
<td>5-FU: 50; epirubicin: 0.5; 4-HC: 2; AP: 30.0 (AND =2 µm)</td>
</tr>
<tr>
<td>FEC + AP-ES</td>
<td>5-FU: 50; epirubicin: 0.5; 4-HC: 2; AP-ES: 32.7 (AND =2 µm)</td>
</tr>
<tr>
<td>FEC + ES</td>
<td>5-FU: 50; epirubicin: 0.5; 4-HC: 2; ES: 2.7</td>
</tr>
<tr>
<td>FEC + ES-RR-SC</td>
<td>5-FU: 50; epirubicin: 0.5; 4-HC: 2; ES-RR-SC: 176</td>
</tr>
</tbody>
</table>

AP-ES, fixed combination of *Andrographis paniculata* and *Eleutherococcus senticosus* (Kan Jang); AND, andrographolide; AP, *Andrographis paniculata*; ES, *Eleutherococcus senticosus*; FEC, fixed combination 5-fluorouracil, epirubicin, and cyclophosphamide; RR, *Rhodiola rosea*; ES-RR-SC, fixed combination of *Eleutherococcus senticosus*, *Rhodiola rosea* and *Schisandra chinensis* (ADAPT-232); 4-HC, 4-hydroperoxycyclophosphamide; 5-FU, 5-fluorouracil.

mRNA microarray hybridization

T98G cells were seeded and attached for 24 hours prior to drug treatment. Cells were treated for 24 hours at various combinations and concentrations of drugs or DMSO as the solvent control (0.5%). Total RNA was then isolated using the InviTrap Spin Universal RNA mini kit (250 preps; Stratec Molecular, Germany). RNA concentrations were determined using the NanoDrop spectrophotometer (NanoDrop Technologies GmbH, USA). Only samples with RNA index values >8.5 were selected for expression profiling. The experiment was performed in duplicate for treated samples and for control samples by the Genomics and Proteomics Core Facility at the German Cancer Research Center in Heidelberg, Germany. Biotin-labeled cRNA samples for hybridization on Illumina Human HT-12 v4 BeadChip arrays were prepared according to Illumina’s recommended sample labeling procedure based on the modified Eberwine protocol. In brief, 250–500 ng total RNA was used for cDNA synthesis, followed by an amplification/labeling step (*in vitro* transcription) to synthesize biotin-labeled cRNA according to the MessageAmp II aRNA amplification kit (Ambion, USA). Biotin-16-UTP was purchased from Roche Applied Science. The cRNA was column purified according to the Total Prep RNA amplification kit and eluted in 60–80 μL water. The cRNA quality was controlled using the RNA nanochip assay on an Agilent Human HT-12 v4 BeadChip. Subsequent hybridization was performed according to the manufacturer’s instruction. Microarray scanning was done using a Beadstation array scanner with the setting adjusted to a scaling factor of 1 and a photomultiplier tube setting of 430. Data extraction was performed for all beads individually, and outliers were removed when the median absolute deviation exceeded 2.5. The mean average signals...
and standard deviations (SDs) were then calculated for each probe. Data analysis was done by normalization of the signals using the quantile normalization algorithm without background subtraction, and differentially regulated genes were defined by calculating the SD differences of a given probe in a one-by-one comparison of samples or groups. The data were further processed using Chipster software (The Finnish IT Center for Science CSC).

IPA

Microarray data were analyzed by IPA (Ingenuity Systems, USA). IPA software relies on the Ingenuity Knowledge Base, a frequently updated database containing biologic and chemical interactions and functional annotations gathered from the literature. In order to obtain information about cellular functions, networks, and affected pathways, IPA offers the Core Analysis tool, which was used for all datasets.

IPA performs different calculations on transcriptomic datasets, including prediction algorithms, and produces results of analyses in a variety of ways, including (I) canonical pathways, which displays the molecules of interest within well-established signaling or metabolic pathways; and (II) upstream analysis, which predicts the upstream regulators (any molecule that can influence the transcription or expression of another molecule) that might be activated or inhibited to explain the expression changes in test datasets.

The interpretation of gene expression data was facilitated by consideration of prior biologic knowledge. IPA software relies on the Ingenuity Knowledge Base, a large gathering of observations with more than 5 million findings manually curated from the biomedical literature or integrated from third-party databases. The network contains 40,000 nodes that represent mammalian genes, molecules, and biologic functions. Nodes are linked by 1,480,000 edges representing experimentally observed cause-effect relationships that relate to gene expression, transcription, activation, molecular metabolism, and binding. Network edges are also associated with a direction (either activating or inhibiting) of the causal effect (72).

To obtain information about the impact of test samples on cellular signaling pathways and networks, for biologic functions and diseases downstream of the genes, whose expression has been altered in a dataset, we used the IPA Core Analysis tool for all tested datasets. Analysis of transcriptomics enabled us to predict regulators that are activated or inhibited based on the distinct up- and downregulation patterns of the expressed genes, and to determine which causal relationships previously reported in the literature are likely to be relevant for the biologic mechanisms underlying the data.

Statistical analysis

Two statistical methods of analysis of gene expression data were used in IPA: (I) gene-set-enrichment method, where differentially expressed genes are intersected with sets of genes that are associated with a particular biological function or pathway providing an ‘enrichment’ score (Fisher’s exact test P value) that measures overlap of observed and predicted regulated gene sets (73,74); (II) The method that based on previously observed cause-effect relationships related to the direction of effects reported in the literature (75,76) providing so called Z-scores assessing the match of observed and predicted up/down regulation patterns (72). The predicted [Z-score >2; or –log (FET P value) >1.3] effects are based on changes of gene expression in the experimental samples relative to the control.

Results

Microarray-based, transcriptome-wide mRNA expression analyses were performed to identify possible targets of the FEC, herbal extracts, and their fixed combination in T98G cells.

FEC significantly (>two-fold) deregulated 23 genes of Nrf2 signaling pathways (Figure 1). Co-incubation with adaptogens induces the upregulation of HMOX1 expression and genes encoding cytoplasmatic transcription factor Kelch-like ECH-associated protein (KEAP1), a key protein involved in the activation of KEAP1-Nrf2-mediated signaling and nuclear transcription factors MAF bZIP transcription factor F and MAF bZIP transcription factor G (Table 2). Moreover, adaptogens prevent FEC-induced downregulation of genes PIK3R2 and RALA encoding Nrf2 upstream signaling proteins PI3K and Ras, as well as genes NQO1, GSR, and GCLC, encoding the expression of cytoplasmatic antioxidant enzymes glutathione-disulfide reductase, NAD(P)H quinone dehydrogenase 1, and glutamate-cysteine ligase catalytic subunit (Table 2). The effects on other gene expressions of Nrf2-mediated signaling are shown in Figure 1 and Table 2.
Discussion

Nrf2 is a principal regulator of redox homeostasis, normally retained in the cytoplasm by KEAP1 (42,77-79). Upon exposure of cells to oxidative stress, Nrf2 is phosphorylated in response to protein kinase C, phosphatidylinositol 3-kinase, and the mitogen-activated protein kinase pathways. After phosphorylation, this complex dissociates, and Nrf2 translocates to the nucleus where it binds with the antioxidant response element (ARE) and triggers the expression of antioxidant and detoxifying genes, including

**Table 2** Effect of FEC on genes involved in the regulation of Nrf2 signaling pathways

<table>
<thead>
<tr>
<th>Gene symbols</th>
<th>Entrez gene name</th>
<th>Cellular function</th>
<th>Location</th>
<th>Type of protein</th>
<th>Fold Change</th>
<th>Signaling regulator</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEAP1</td>
<td>Kelch-like ECH associated protein 1</td>
<td>Cytoplasm</td>
<td>Transcription regulator</td>
<td>1.72</td>
<td>1.72</td>
<td>2.04</td>
</tr>
<tr>
<td>HMOX1</td>
<td>Heme oxygenase 1</td>
<td>Cytoplasm</td>
<td>Enzyme</td>
<td>3.23</td>
<td>4.76</td>
<td>5.70</td>
</tr>
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<td>SOD2</td>
<td>Superoxide dismutase</td>
<td>Cytoplasm</td>
<td>Enzyme</td>
<td>2.04</td>
<td>2.81</td>
<td>1.98</td>
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<tr>
<td>DNAJB9</td>
<td>DnaJ heat shock protein family (Hsp40) member B9</td>
<td>Nucleus</td>
<td>Repair</td>
<td>1.82</td>
<td>1.82</td>
<td>1.82</td>
</tr>
<tr>
<td>MAFF</td>
<td>MAF bZIP transcription factor F</td>
<td>Nucleus</td>
<td>Transcription regulator</td>
<td>1.98</td>
<td>1.98</td>
<td>1.98</td>
</tr>
<tr>
<td>MAFG</td>
<td>MAF bZIP transcription factor G</td>
<td>Nucleus</td>
<td>Transcription regulator</td>
<td>1.82</td>
<td>1.82</td>
<td>1.82</td>
</tr>
<tr>
<td>AKR1A1</td>
<td>Aldo-keto reductase family 1 member A1</td>
<td>Cytoplasm</td>
<td>Enzyme</td>
<td>1.72</td>
<td>1.72</td>
<td>1.72</td>
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<tr>
<td>ACTG1</td>
<td>Actin gamma 1</td>
<td>Nucleus</td>
<td>Transcription regulator</td>
<td>1.98</td>
<td>1.98</td>
<td>1.98</td>
</tr>
</tbody>
</table>

**Figure 1** Heatmap showing the effects of test samples on upregulation (red) and downregulation (green) of the gene expression of the nuclear factor erythroid 2-related factor-2 (Nrf2) signaling pathway in neuroglia cells. ADAPT, fixed combination of *Eleutherococcus senticosus*, *Rhodiola rosea* and *Schisandra chinensis*; AND, andrographolide; AP, *Andrographis paniculata*; ES, *Eleutherococcus senticosus*; FEC, fixed combination 5-fluorouracil, epirubicin, and cyclophosphamide; KJ, fixed combination of *Andrographis paniculata* and *Eleutherococcus*.
<table>
<thead>
<tr>
<th>Gene symbols</th>
<th>Entrez gene name</th>
<th>FEC</th>
<th>FEC + AND</th>
<th>FEC + AP</th>
<th>FEC + AP-ES</th>
<th>FEC + ES</th>
<th>FEC + ES-RR-SC</th>
<th>Location</th>
<th>Type of protein</th>
<th>Cellular function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3R2/P8K</td>
<td>Phosphoinositide-3-kinase regulatory subunit 2</td>
<td>-1.66</td>
<td>-2.08</td>
<td>-1.67</td>
<td>Cytoplasm</td>
<td>Kinase</td>
<td>Signaling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RALA/Ras</td>
<td>Ras-related protein Ral-A</td>
<td>-1.67</td>
<td>2.60</td>
<td>2.59</td>
<td>Plasma membrane</td>
<td>GTPase</td>
<td>Signaling</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GSR/GSR</td>
<td>Glutathione-disulfide reductase</td>
<td>-1.85</td>
<td>2.01</td>
<td>3.62</td>
<td>Cytoplasm</td>
<td>Enzyme</td>
<td>Antifox</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCLC/GCLC</td>
<td>glutamate-cysteine ligase catalytic subunit</td>
<td>-1.93</td>
<td></td>
<td></td>
<td>Cytoplasm</td>
<td>Enzyme</td>
<td>Detox</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOS/Fos</td>
<td>Fos proto-oncogene, AP-1 transcription factor subunit</td>
<td>-3.41</td>
<td>-2.44</td>
<td>-2.56</td>
<td>-2.48</td>
<td>2.04</td>
<td>1.87</td>
<td>Nucleus</td>
<td>Transcription regulator</td>
<td>Signaling</td>
</tr>
<tr>
<td>CAT/CAT</td>
<td>Catalase</td>
<td>-1.69</td>
<td>-2.15</td>
<td>-2.12</td>
<td>-1.92</td>
<td>1.74</td>
<td>1.78</td>
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<td>Enzyme</td>
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<tr>
<td>PRKCA/PKC</td>
<td>Protein kinase C alpha</td>
<td>-1.98</td>
<td>-1.92</td>
<td>-2.40</td>
<td>-2.21</td>
<td></td>
<td></td>
<td>Cytoplasm</td>
<td>Enzyme</td>
<td>Signaling</td>
</tr>
<tr>
<td>FRS2</td>
<td>Fibroblast growth factor receptor substrate 2</td>
<td>1.97</td>
<td>1.70</td>
<td>1.89</td>
<td>2.17</td>
<td>-1.77</td>
<td></td>
<td>Plasma Membrane</td>
<td>Kinase</td>
<td>Signaling</td>
</tr>
<tr>
<td>HSPB8</td>
<td>Heat shock protein family B (small) member 8</td>
<td>2.39</td>
<td>3.18</td>
<td>4.94</td>
<td>4.89</td>
<td>1.75</td>
<td></td>
<td>Cytoplasm</td>
<td>Kinase</td>
<td>Repair</td>
</tr>
<tr>
<td>SOD2/SOD</td>
<td>Superoxide dismutase 2</td>
<td>2.27</td>
<td>2.27</td>
<td>2.63</td>
<td>2.60</td>
<td>-1.74</td>
<td></td>
<td>Cytoplasm</td>
<td>Enzyme</td>
<td>Antifox</td>
</tr>
<tr>
<td>ABCC4</td>
<td>ATP binding cassette subfamily C member 4</td>
<td>-1.89</td>
<td>-1.71</td>
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<td>-2.27</td>
<td>-2.22</td>
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<td>Plasma membrane</td>
<td>Transporter</td>
<td>Detox</td>
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<td>DnaJ heat shock protein family (Hsp40) member C10</td>
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<td>-1.97</td>
<td>-2.01</td>
<td>Nucleus</td>
<td>Other</td>
<td>Repair</td>
</tr>
</tbody>
</table>

Nrf2, nuclear factor erythroid 2-related factor-2; AP-ES, fixed combination of Andrographis paniculata and Eleutherococcus senticosus (Kan Jang); AND, andrographolide; AP, Andrographis paniculata; ES, Eleutherococcus senticosus; FEC, fixed combination 5-fluorouracil, epirubicin, and cyclophosphamide; RR, Rhodiola rosea; ES-RR-SC, fixed combination of Eleutherococcus senticosus, Rhodiola rosea and Schisandra chinensis (ADAPT-232); 4-HC, 4-hydroperoxycyclophosphamide; 5-FU, fluorouracil.
SOD, GST, NQO1, and HMOX1 (42,77). Therefore, the activation of Nrf2 translocation or the upregulation of gene expression resulting in the activation of the Nrf2 mediated signaling pathway is the key mechanism of cellular defense response associated with the antioxidant effects of medicinal plants (43-45), and particularly of adaptogenic plants, which are useful in stress- and aging-related diseases (40,41,78).

Figures 1, 2 show that FEC inhibits the Nrf2 signaling pathway via the deregulation of expression of 24 genes, whereas adaptogens prevent or mitigate FEC-induced deregulation of a number of genes involved in the predicted activation of Nrf2-mediated signaling and expression of antioxidant and detoxifying genes, including SOD, GST, NQO1, and HMOX1 (Figures 3,4).
Figure 3 Effect of adaptogens on FEC-induced inhibition of Nrf2 signaling pathway: (A) Predicted activation (brown lines and red circles) of nuclear factor erythroid 2-related factor-2 (Nrf2) canonical pathway by *Eleutherococcus senticosus* (ES); (B) predicted inhibition (blue lines and green circles) of Nrf2 canonical pathway by fixed combination 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) + ES; (C) predicted activation of Nrf2-mediated signaling by FEC-ES-*Schisandra chinensis* (SC)-*Rhodiola rosea* (RR).
Figure 4 Andrographolide (AND), Andrographis paniculata (AP), and AP–Eleutherococcus senticosus (ES) prevents the chemotherapy fixed combination 5-fluorouracil, epirubicin, and cyclophosphamide (FEC)-induced downregulation of genes and the activated production of nuclear factor erythroid 2-related factor-2 (Nrf2)-mediated signaling proteins and antioxidant and detoxifying proteins, and upregulates the genes involved in oxidation damage reduction. Upregulated genes are shown in red, whereas downregulated genes are shown in green. Predicted activation (brown lines) of Nrf2 canonical pathway by AND + FEC (A), AP + FEC.
Conclusions

The results of the present study suggest that the beneficial effects of adaptogens on impaired neuronal and cognitive functions are due to mitigating oxidative stress-induced cellular damage by multitarget regulation of redox homeostasis via the regulation of gene expression, activating Nrf2 signaling pathway proteins and modulating antioxidant, metabolizing, and detoxifying enzymes.

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/lcm-20-24

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). No ethic committee’s approval is required in Germany for in vitro experiments of commercially available T98G human glioblastoma cell line (Merck KGaA, Darmstadt, Germany).

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