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Computational Docking Study of Phytochemicals against Ovarian and Uterine Disorder-Associated Protein Targets

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ABSTRACT:

Background: Menstrual disorders are widespread and often inadequately managed by conventional therapies. Ayurvedic formulations such as Aloes Compound have shown clinical efficacy but lack mechanistic validation. **Objective:** To explore molecular interactions of phytochemicals from Aloes Compound with key ovarian and uterine receptor targets. **Methods:** Twenty-six phytochemicals were docked against six reproductive receptors (FSHR, ER α , ER β , PR, PGE2, GPR30) using Auto Dock Vina. Docking validation was done by native ligand re-docking and active site overlap analysis. **Results:** Steroidal compounds (friedelin, stigmasterol, β -sitosterol) showed highest affinity with FSHR and ER α ; flavonoids (rutin, luteolin) showed strong multi receptor activity. Active site overlap confirmed pharmacological relevance. **Conclusion:** The study provides mechanistic insight into the clinical efficacy of an Aloes Compound, suggesting multi target modulation of reproductive pathways consistent with Ayurvedic claims.

KEYWORDS:

Menstrual disorders; Fertility regulation; Molecular docking; Multi target therapeutics.

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INTRODUCTION:

Menstrual disorders such as amenorrhea, dysmenorrhea, oligomenorrhea, and irregular cycles affect a large number of women throughout their reproductive years. These conditions can disrupt daily activities, reduce overall well-being, and may contribute to infertility or long-term reproductive issues. Estimates indicate that nearly 70–80% of women experience menstrual pain or irregularity at some point in their lives, showing how widespread these problems are. Although hormonal therapy and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used, they mainly provide temporary relief and may cause side effects such as metabolic changes, gastrointestinal discomfort, and in some cases, negative effects on fertility. Because of these limitations, there is growing interest in safer approaches that can act on multiple pathways involved in menstrual and reproductive health. Ayurvedic medicine has long relied on herbal combinations to regulate menstrual cycles, ease pain, and support fertility. The Aloes Compound studied here is rooted in classical texts such as Bhavaprakasha Nighantu [1]. These sources mention the therapeutic value of botanicals like Aloes (*Aloes indica*), Majith (*Rubia cordifolia*), Hurmal (*Peganum harmala*), Jeevanti (*Leptadenia reticulata*), and Kamboji (*Breynia patens*) for various gynecological and reproductive concerns. Their long-standing use reflects centuries of practical experience. However, despite extensive traditional knowledge, the exact molecular mechanisms behind their effects remain unclear. Understanding these mechanisms is important for building scientific support for such formulations. Modern computational tools now make it possible to explore how plant-derived compounds may interact with specific receptors in the body, offering a bridge

between traditional wisdom and molecular evidence. Many of the individual herbs in this formulation have already been described for their roles in women's health. *Aloes indica* is traditionally known as a uterine stimulant and is commonly used in conditions like amenorrhea and dysmenorrhea [2]. Its anthraquinone compounds may help improve uterine tone and support cycle regularity [3]. *Rubia cordifolia* is well known for managing excessive or irregular uterine bleeding and menstrual discomfort, and recent studies also suggest benefits in PCOS [4,5]. *Peganum harmala* contains alkaloids that influence reproductive activity, including effects on sexual behavior and gametogenesis [6]. *Leptadenia reticulata* (Jeevanti) has been traditionally associated with female reproductive health, and early research indicates possible anti-implantation activity [7]. *Breynia patens* and the resin from *Balsamodendron myrrh* are also used in several gynecological preparations, with clinical reports supporting their usefulness in cases such as incomplete abortion [8,9]. Thus, herbal medicines continue to play an important role in menstrual health across cultures, as shown in global ethnopharmacological surveys [10]. For this work, six key protein receptors were selected due to their well-known roles in ovarian and uterine function. These include the follicle-stimulating hormone receptor (FSHR), estrogen receptors ER α and ER β , the progesterone receptor (PR), the prostaglandin E2 receptor (PGE2), and the G-protein-coupled estrogen receptor (GPR30). These receptors collectively influence follicle development, ovulation, endometrial growth, uterine contractility, implantation, and hormonal signaling [11–14]. If the phytochemicals present in the formulation interact with these targets, they may help support menstrual balance and improve fertility-related outcomes. In this study,

molecular docking and visualization techniques were used to explore how the phytochemicals from the formulation bind to these six reproductive receptors. By examining these interactions, the study aims to offer a clearer mechanistic understanding of the formulation's traditional uses and to place its effects within the wider context of modern molecular pharmacology.

Material & Methods

Active Compounds Library

A complete library of twenty-six bioactive phytochemicals was compiled from six medicinal plants traditionally used in Ayurveda for menstrual and fertility-related disorders: *Aloes indica*, *Balsamodendron myrrh*, *Rubia cordifolia*, *Peganum harmala*, *Leptadenia reticulata*, and *Bryenia patens*. Compounds included anthraquinones, terpenoids, alkaloids, flavonoids, sterols, and phenolic acids such as Aloin A, Aloe-emodin, Lupeol, Chrysophanol, Furanoedesma-1,3-diene, Curzerene, Lindestrane, Sesquiterpenes, Alizarin, Purpurin, Rubiadin, Harmine, Harmaline, Harmalol, Vasicinone, Quercetin, Rutin, Luteolin, Diosmetin, Stigmasterol, β -Sitosterol, Gallic acid, Ellagic acid, p-Coumaric acid, Ferulic acid, and Friedelin. Molecular structures were downloaded in 3D conformer SDF format from the PubChem database.

Target Selection

The receptors selected for this study were chosen because of their well-known functions in ovarian activity, uterine readiness for implantation, and the broader mechanisms involved in menstrual disorders and fertility. Each receptor represents an important control point in processes such as follicular development, hormonal signaling, implantation, and uterine muscle regulation. Selected Receptors are; FSHR (Follicle-Stimulating Hormone Receptor), ER α and ER β (Estrogen Receptors), GPR30/GPER1 (G Protein-Coupled Receptor), PGE2

(Prostaglandin E2 Receptor), PR (Progesterone Receptor).

Receptor and Ligand Preparation

Three-dimensional structures of the selected protein targets were retrieved from the Protein Data Bank (PDB), with preference for high-resolution entries and functionally relevant conformations. Receptor structures were firstly processed in PyMOL (version 3.0.5) and UCSF Chimera (version 1.19), where water molecules, heteroatoms, and alternate chains were removed and receptor files were prepared for docking using the Dock Prep utility [15,16]. Ligands in SDF format from PubChem were energy-minimized and converted to PDBQT format using Open Babel before docking [17].

Molecular Docking

Docking was performed using AutoDock Vina integrated in PyRx (version 0.8) [18]. A blind docking strategy was applied, covering the entire receptor surface to avoid bias toward predefined binding pockets. Exhaustiveness was fixed at 8 to balance efficiency and accuracy. For each ligand-receptor pair, binding affinities were recorded in kcal/mol, and the lowest-energy conformation was selected for analysis [19].

Validation by Native Ligand Re-docking

To ensure reliability of the docking protocol, native ligands co-crystallized with their respective receptors were re-docked using the same docking parameters. Active site were then identified based on native ligand binding pockets and only phytochemicals occupying these validated sites were prioritized for further screening. Structural visualization and alignment of docked phytochemicals with native ligands (as a complex) were carried out in PyMOL, confirming site-specific interactions [15].

Results

Initial Docking and Screening

Docking analysis of the twenty-six selected phytochemicals against the six reproductive

receptors produced binding scores ranging from -5.1 to -10.4 kcal/mol. To focus on compounds with stronger pharmacological relevance, a cut-off value of -8.5 kcal/mol was used. Applying this filter reduced the list to

fourteen molecules. Most of the higher-affinity hits belonged to steroidal, flavonoid, and anthraquinone groups, indicating that these structural classes contributed most consistently to strong receptor engagement.

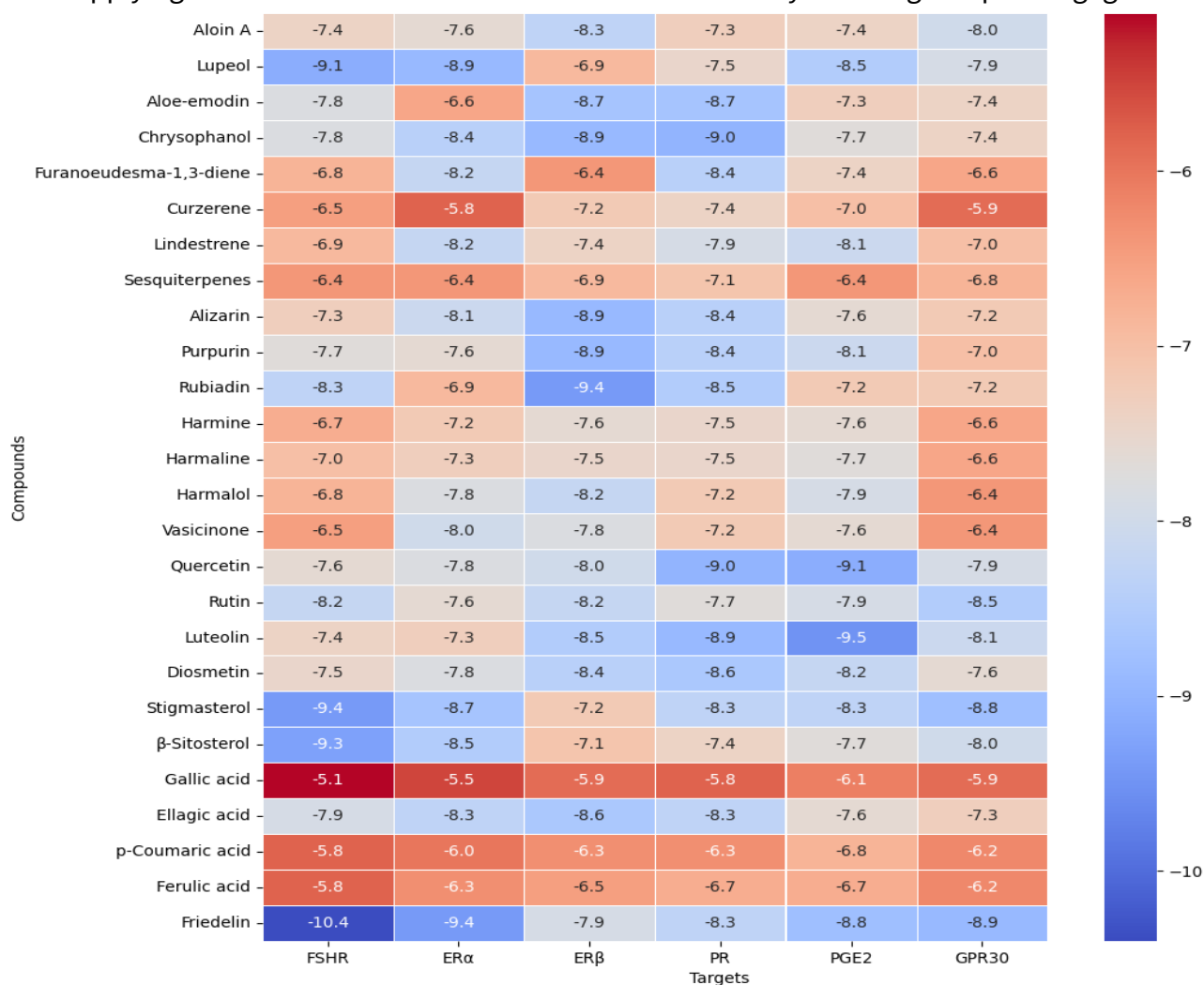


Figure 1: Heatmap for Docking Poses with affinities.

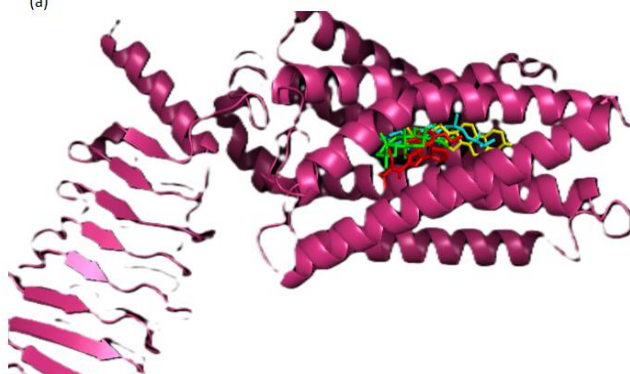
Active-Site Validation by Re-docking
Several compounds met both selection criteria: high affinity (≤ -8.5 kcal/mol) and correct placement within the native ligand pocket. For FSHR, β -sitosterol, stigmasterol, and friedelin aligned with the native ligand's binding site and showed strong binding scores (-9.3 to -10.4 kcal/mol). In ERα, sterols including β -sitosterol, lupeol, stigmasterol, and friedelin consistently occupied the receptor's natural binding region. The ERβ receptor showed a different preference. Compounds such as aloe-emodin,

chrysophanol, alizarin, and purpurin docked selectively within the active pocket, highlighting a pattern where anthraquinones appear more suited for ERβ targeting. For PR, chrysophanol, aloe-emodin, and diosmetin aligned with the native cavity, whereas lupeol showed comparable positioning in the PGE2 receptor pocket. Other phytochemicals also entered the active sites during docking, but because their affinities fell below the -8.5 kcal/mol threshold, they were not prioritized in subsequent analysis. Overall, the overlap between phytochemical docking poses and

native ligand positions supports the reliability of the docking protocol and strengthens the likelihood that the high-

affinity compounds represent biologically meaningful interactions

(a)



(b)



Figure 2: 3D interaction of (a) FSHR with Beta-sitosterol (Blue), Stigmasterol (Cyan), Friedlin (Green) and Control (Red) & (b) ERα with Beta-sitosterol (Blue), Lupeol (Yellow), Stigmasterol (Cyan), Friedlin (Green) and Control (Red)

(a)

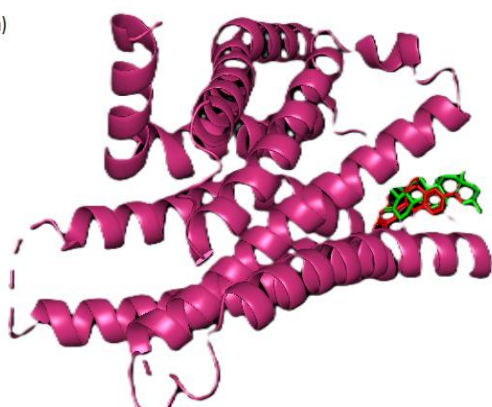


(b)



Figure 3: 3D interaction of (a) ERβ with Aloe emodin (Grey), Chrysophanol (Pink), Purpurin (Lime) and Control (Red) & (b) PR with Chrysophanol (Yellow), Aloe emodin (Cyan), Diosmetin (Blue) and Control (Red)

(a)



(b)

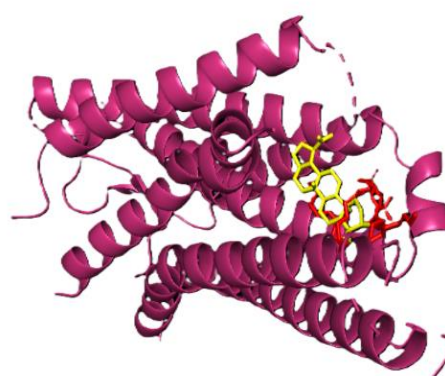


Figure 4: 3D interaction of (a) GPR30 with Friedlin (Green) and Control (Red) & (b) PGE2 with Lupeol (Yellow) and Control (Red)

Class-Specific Trends and Key Observations
A clear pattern emerged when compounds were grouped by chemical classes. Steroidal molecules such as friedelin, β -sitosterol, stigmasterol, and lupeol demonstrated strong and consistent binding to FSHR, ER α , ER β , GPR30, and PGE2, suggesting their importance in supporting ovarian steroidogenesis and reproductive signaling. Flavonoids like luteolin and rutin showed

activity across multiple receptors, particularly PR, indicating possible roles in uterine modulation, inflammation control, and broader hormonal balance. Anthraquinones including aloë-emodin, chrysophanol, and alizarin showed a preference for ER β and PR, which may reflect their more targeted role in maintaining estrogen–progesterone balance.

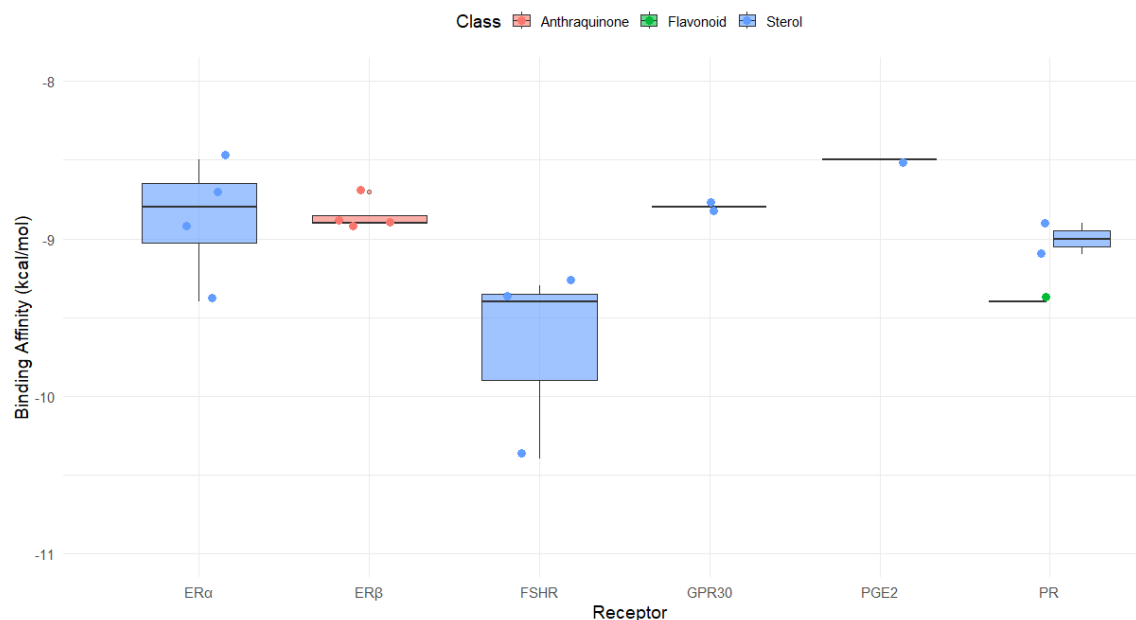


Figure 5: Class Specific Trends

Together, these trends show that different classes of compounds contribute in complementary ways: sterols act as strong hormonal receptor binders, flavonoids provide versatile multi-target interactions, and anthraquinones deliver more focused regulatory input. This combined action may underlie the wide therapeutic usefulness of the Aloes Compoundin managing menstrual and fertility-related conditions.

DISCUSSION:

This study represents the first comprehensive in-silico evaluation of the twenty-six phytochemicals present in the classical Ayurvedic formulation against six protein targets central to ovarian and uterine health. The docking results consistently highlighted

the strong binding potential of steroidal phytoconstituents (friedelin, stigmasterol, β -sitosterol), flavonoids (quercetin, luteolin, rutin), and anthraquinones (alizarin, rubiadin, chrysophanol) across multiple receptors, with particularly high affinities observed for FSHR, ER α , and PGE2. Subsequent re-docking and comparison with native ligands further validated that several of these phytochemicals co-localize within the active binding pockets, reinforcing their likelihood of physiologically relevant activity. To contextualize these findings, the corresponding native ligands for each target receptor are outlined in Table 1, serving as pharmacological benchmarks for comparison.

Table 1 : Receptor targets and their corresponding native ligands (Control).

PDB ID	Target Protein Receptor	Native Ligand (Control)
8I2H	Follicle Stimulating Hormone Receptor (FSHR)	21 F Or O6F
3ERT	Estrogen Receptor α (ER α)	4-Hydroxytamoxifen
1QKM	Estrogen Receptor β (ER β)	Genistein
1SR7	Progesterone Receptor (PR)	Mometasone furoate
6AK3	Prostaglandin E2 Receptor (PGE2)	POV
8XOG	G-protein coupled Estrogen Receptor 30 (GPR30)	G-36

Friedelin [Plant: Kamboji], Stigmasterol [Plant: Jeevanti] and β -sitosterol [Plant: Jeevanti] showed strong binding at the FSHR, similar to a known positive allosteric agonist, known as -N-tert-butyl-N-ethyl-8-methoxy-9-propan-2-yloxy-1-thiophen-2-yl-5,6-dihydroimidazo[5,1-a]isoquinoline-3-carboxamide i.e. 21 F or O6F indicating elevated receptor-hormone interactions [20]. Increased granulosa cell reactivity is indicated by this interaction profile, which makes follicular recruitment and selection easier. By functionally counteracting anovulation and abnormalities in cycle duration, such modulation may have therapeutic implications for disorders like amenorrhea and oligomenorrhea.

Across nuclear estrogen receptors, a complementary pattern was found. ER α was bound by β -sitosterol, stigmasterol, lupeol [Plant: Aloes] and Friedelin. Their interactions mimic allosteric antagonism, which can suppress excessive proliferative signals [21]. On the other hand, for ER β anthraquinones Aloe emodin [Plant: Aloes], Chrysophanol [Plant: Aloes], Alizarin [Plant: Majith], and Purpurin [Plant: Majith] supported tissue-selective estrogenicity and anti-proliferative checks by preferentially engaging ER β as partial agonists [22]. By limiting overstimulation and preserving endocrine tone, this differential binding together forecasts the restoration of estrogen equilibrium, and is particularly relevant for

irregular cycles and endometrial dysregulation.

Overlapping of Friedelin with control's binding site at GPR30 suggests antagonist profile which may result in suppression of key estrogen-dependent signaling cascades, including PI3K-Akt, calcium mobilization, and ERK1/2 pathways, collectively reduces estrogen-driven cell proliferation, survival, and rapid signaling responses in ovarian and uterine tissues [23]. As a result, these actions may help control abnormal cell growth, inflammation and pain associated with estrogen over-activity. Chrysophanol, Aloe emodin, and Diosmetin [Plant: Jeevanti] native site binding at PR indicates enhanced endometrial receptivity, regulation of uterine excitability, and intensified luteal signaling. Clinically, this could assist implantation physiology, lessen dysmenorrhea, and improve luteal-phase insufficiency through the uterine-calming effects of progesterone [24]. Lupeol's presence in the PGE2 receptor pocket suggests a reduction in prostaglandin induced nociception and hyper contractility. This process is consistent with cramp relief and could help normalize pain related to cycle [25].

CONCLUSION:

The present study provides mechanistic insights into the molecular basis of the clinical efficacy reported for the classical Ayurvedic formulation an Aloes Compound. Traditionally prescribed for menstrual and

fertility related disorders, this polyherbal medicine has demonstrated positive outcomes in clinical settings, including trials conducted at various places in India. These trials reported improvements in menstrual regularity, symptomatic relief, and enhancement of fertility indices. However, until now, the formulation lacked a systematic molecular-level explanation to support its therapeutic activity.

This work proposes a mechanistic rationale for how the multi constituent, Aloes Compound may normalize menstrual physiology and improve fertility indices via coordinated, receptor level modulation. High-affinity phytochemicals (≤ -8.5 kcal/mol) that also co-localize with native ligand binding pockets provide the strongest evidence for pharmacologically meaningful interactions.

The present work is limited to computational predictions of ligand–receptor interactions and does not account for pharmacokinetic, metabolic, or in-vivo physiological variables. Future research involving in-vitro receptor binding, cellular validation and clinical correlation will be essential to substantiate these computational findings and establish translational relevance.

Taken together, this integrative approach underscores the value of Ayurvedic formulations as multi target therapeutics and supports their positioning as evidence based interventions for reproductive health.

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Conflict of interest

This research was conducted as part of the ongoing scientific initiatives of Alarsin, Mumbai. The authors declare that there are no conflicts of interest beyond their professional affiliation with the organization.

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