Paronychia Argentea: A Critical Comprehensive Review on its Diverse Medicinal Potential and Future as Therapeutics

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ABSTRACT

Background: Paronychia argentea has been used since long as a traditional medicine for the treatment of diabetes, kidney stones, anti-microbial and many other human diseases. However, the plant has not been explored much. In the present scenario of drug resistance and toxicity associated with available drugs, there is a need for elaborated studies of plants like Paronychia argentea which has been used as folk medicines. Aim and Objectives: The present article is focused on reviewing the ethnopharmacology, phytochemistry, traditional usage, pharmacological activities, of Paronychia argentea which has been used in traditional medicinal system for ages. The aim of the study was to assess the ethnopharmacological usage of this plant and to explore therapeutic potentials and future opportunities for research.

Materials and Methods: Information on the traditional usage and studies of the Paronychia argentea was gathered from from various journals, MSc dissertation, conference abstract, local books. Various search engines including Google Scholar, Baidu Scholar, Elsevier, ACS, Pubmed, Web of Science, CNKI and EMBASE were used to collect the information along with libraries. Results: Paronychia argentea has played an important role in traditional medicines in Algeria, Portugal, Israel and Jordan. The aerial parts of this plant are used as diuretics in Algerian traditional medicines and are used as antiurolithiasis. Leaf decoction of this plant is also used as diuretic. Paronychia argentea has been used as analgesic, treatment of stomach ulcer, anorexia, and flatulence in Portugal. Scientific studies on extracts of Paronychia revealed a wide range of pharmacological activities including anti-microbial activity, anti-oxidant, nephroprotective activity. Moreover, few reports have given contradictory data for usage of Paronychia when compared with its traditional usage. As in the case of alpha-amylase inhibitory efficacy of PA, it was observed that PA inhibits alpha-amylase activity but later on it was proven that PA does not have a hypoglycemic effect. Main bioactive metabolites present in this plant include alkaloids, flavonoids, volatile oils, etc. Conclusions: Based on this review, there are evidences from various studies regarding pharmacological effects of this plant as nephroprotective, anti-oxidant, anti-microbial activity. Some indications from in vitro studies have confirmed the inhibitory activity of this plant extract against alpha amylase enzyme. The available literature showed that most of the activities of the Paronychia can be accredited to the flavonoids present in them. Data regarding mechanisms of action of this plant along with pharmacokinetics, toxicology studies is still limited, which indicate the need of such studies for the clinical usage of this plant.

Key words: Paronychia argentea, Nephroprotective, Anti-microbial, Anti-oxidant, Ulcerative colitis, Bioactivity, Oxidative stress, Herbal medicine, Therapeutic value.

INTRODUCTION

Herbal medicines have been used in almost all the countries, since the beginning of history. A vast repository of such plants with medicinal values has not been explored much. There is need to establish a common platform which has the information regarding traditional original usage and local names of such plant along with other therapeutic efficacies of such plants. It is very unfortunate that in the current technology world, this area has not been explored much. However, renewed interest in this area has arisen, due to emerging problem of drug resistance and toxicity associated with available drugs. One such plant with potential therapeutic value is Paronychia argentea.

Botanical classification and habitat

Paronychia argentea (PA) was first described by Jean-Baptiste Lamarck.¹ Its taxonomy is as follows:

Superdivision: Spermatophyta
Division: Angiospermae
Class: Dicotyledoneae
Family: Caryophyllaceae
Genus: Paronychia

PA is a Perennial plant with stems spreading on the ground. It is in leaf all year and flowers appear from July to August. Flowers of this plant are small and arranged in heads surrounded by hyaline bracts. It is a hermaphrodite species and pollination occurs by
in California, 3 at Akhanasira range reserve of Jordan, 4 in Spain. 5 at Al Mansora in Al-Jabal Al-Akhdar-Libya. It has also been reported along with its usage to treat kidney stones, diabetes and cardiovascular diseases. It was also used as a blood purifier. 12 In Portugal, PA has been used as analgesic, treatment of stomach ulcer, anorexia and flatulence. 13 Decoction of aerial parts of PA is being used in Jordan as traditional medicine known as ‘rejel el-hamama’ or ‘shooshet el-rae’ for UTI infections and other diseases 14 Lev. 15 The tisane of its leaves is used for treating diabetes in Israel. 16, 17

**Traditional medicinal value**

PA is the most common plant used abundantly in conventional medicines in Algeria and is popularly known as Arabic tea (Kassaretlahdjer, Fettatelahdjer or Bissatelmoulouk). PA have high content of flavonoids isorhamnetin, quercetin and luteolin. 3 The aerial parts of this plant are used in as diuretic in Algerian traditional medicines. It is also used for curing renal diseases, especially as antiurithiasis. 5 It has been reported that PA also has digestive, 9 hypoglycemic, 9 and antimicrobial activity. 10 Diuretic potential of PA has been described by Dafni et al. 11 along with its usage to treat kidney stones, diabetes and cardiovascular diseases. It was also used as a blood purifier. 12 In Portugal, PA has been used as analgesic, treatment of stomach ulcer, anorexia and flatulence. 13 Decoction of aerial parts of PA is being used in Jordan as traditional medicine known as ‘rejel el-hamama’ or ‘shooshet el-rae’ for UTI infections and other diseases 14 Lev. 15 The tisane of its leaves is used for treating diabetes in Israel. 16, 17

**HPLC analysis of Paronychia argentea**

A study based on High pressure liquid chromatography (HPLC) method of analysis was planned to determine the two major constituents of Paronychia argentea dry extract (PAE) (Figure 1). This was based on establishing a chromatographic method to analyse, determine and standardize the two main chemical constituents in PAE viz., vanillic acid and luteolin (Table 1). It was observed that luteolin and vanillic acid were completely separated from other components in the PAE with an Rf value of 1.3 and 5.7 min. respectively. Two separate peaks of both these compounds were concurrently separated and were determined from other components in PAE collected from the plants present in Jordan area. The concentration of Luteolin was found to be 0.4 % and that of vanillic acid to be 0.1% using a validated chromatographic method of analysis. 19 Another detailed study was carried out to do the psychochemical characterization of PA collected from the region of Adekar (West of Bejaia, Algeria). The main aim of this study was to characterize the flavonoid profile of PA along with evaluation of antioxidant property of the ethanolic extract, decoction and infusion of PA aerial parts. HPLC along with diode array detection and electrospray ionization mass spectrometry was used to analyze the flavonoid contents in PA (Figure 2). In order to identify and estimate the antioxidant property of the plant extracts, four methods were used. These included evaluations of the reducing power along with estimation of lipid peroxidation inhibition and scavenging of free radicals like DPPH• and NO•. Results showed eleven compounds of which six were characterized for the first time. The six new compounds isolated were isorhamnetin-3-O-dihexoside, quercetin-3-O-glucoside, quercetinmethyl ether-O-hexoside, quercetin, jaceosidin and isorhamnetin. It was found that highest flavonoid content was present in the ethanolic extract followed by decoction and infusion respectively. Protocol standardized by Hseu et al. 19 was used to evaluate the reducing power of extracts. DPPH• free radical scavenging activity was determined using protocol by Suja et al. 20 and to evaluate the inhibition of lipid peroxidation activity, method by Chan et al. 21 was used. It was found that best antioxidant activity was shown by decoction for all the four assays. The data strengthened the antioxidant potential of PA for therapeutic usage. 22 Another study identified two new oleanane saponins and one new flavonol glycoside along with 6 flavonoids which have been identified in aerial parts of PA previously also. The structure of the compounds was elucidated using 1D and 2D NMR. 22 The various classes of phytochemicals present in the Paronychia argentea were shown in Table 2.

**Bioactivity**

PA possesses potential therapeutic properties such as anti-inflammatory, antidiabetic, nephroprotective etc. This section focuses in detail on its various medicinal properties along with the shortcomings of the studies because of which this plant has not reached much up to clinical trials and clinics.

**Nephroprotective**

Urinary stone is one of the most common disorder and percentage reappearance of these stones is very high in male followed by female. 24 The main constituent analyzed in these stones is Calcium oxalate (80%). 22 Formation of a kidney stone is a complex process involving various physicochemical events in succession. 22 Standard treatment regimen for eliminating kidney stones includes extracorporeal shockwave lithotripsy (ESWL) and drug treatment. However, ESWL is related to severe side effects including traumatic effects of shock waves, persistence of residual stone fragments, infection. It may also cause renal injury, effect the functions of kidney, haemorrhage and hypertension. 23, 24 These side effects emphasize the need of alternative medicinal approaches, of which medicinal plants may be the safest.
Table 1: Compounds identified in Paronychia argentea.

| Sno. | Method used | Chemical compound identified | Habitat of Paronychia argentea samples | Content of flavonoids in the ethanolic extract, decoction and infusion of P. argentea (data are expressed as mg/g DM) |
|------|-------------|-----------------------------|--------------------------------------|-------------------------------------------------------------------------------------------------------------|
| 1.   | High pressure liquid chromatography (HPLC) | Vanillic acid | Plant material of P. argentea, aerial part, was collected on April 2016 from Ajloun area, Jordan. | 18 ± 0.3 1.2 ± 0.1 <LOD |
| 2    | HPLC-UV/DAD and HPLC–ESI-MS | Luteolin | P. argentea aerial parts were collected in the region of Adekar (West of Bejaia, Algeria) | 3.2 ± 0.1 1.4 ± 0.1 <LOD |
| 3    | HPLC-UV/DAD and HPLC–ESI-MS | Quercetin-3-O-(glucosyl)galactoside | Ethanol extract, decoction, infusion | 4.3 ± 0.3 1.2 ± 0.1 <LOD |
| 4    | | Quercetin-3-O-[(2′−acetyl)glucosyl]galactoside | | 3.2 ± 0.1 1.4 ± 0.1 <LOD |
| 5    | | Quercetin-3-O-galactoside | | 10.3 ± 0.3 2.9 ± 0.2 <LOD |
| 6    | | Quercetin-3-O-glucoside | | 1.8 ± 0.1 0.6 ± 0.1 <LOD |
| 7    | | Quercetinmethylether-O-hexoside | | 2.7 ± 0.1 1.0 ± 0.1 <LOD |
| 8    | | Isorhamnetin-3-O-glucoside | | 1.0 ± 0.1 <LOQ <LOD |
| 9    | | Jaceosidin-7-O-glucoside | | <LOQ 0.6 ± 0.1 0.2 ± 0.1 |
| 10   | | Quercetin | | <LOQ <LOD <LOD |
| 11   | | Jaceosidin | | <LOD 0.1 ± 0.1 <LOQ |
| 12   | | Isorhamnetin | | <LOQ <LOD <LOD |

Abbreviation: limit of detection (LOD) and the limit of quantification (LOQ)

Figure 3: Mechanism of anti-oxidant potential of PA.
Various medicinal plants have been used to treat urolithiasis. PA has been used traditionally for its diuretic property and curing kidney other kidney ailments in Algeria. However, very few detailed studies have been done to evaluate its potential along with toxicity studies. A detailed study was performed to evaluate the renal protective and antiurolithiatic efficacy of *Paronychia argentea* (PA) was evaluated using two extracts, namely aqueous extract (PAA) and butanolic extract (PAB). Aerial parts of this plant was used to prepare both the extracts using two extracts, namely aqueous extract (PAA) and butanolic extract (PA) was evaluated antiurolithiatic efficacy of *Paronychia argentea*. Both the extracts were administered orally in which oxalocalciclithiasis was induced by an intraperitoneal injection and evaluate the effect on reduction in calculi aggregation in Wistar rats (PAB). Aerial parts of this plant was used to prepare both the extracts and evaluate the effect on reduction in calculi aggregation in Wistar rats in which oxalocalciclithiasis was induced by an intraperitoneal injection of sodium oxalate (NaOx). Both the extracts were administered orally for 28 days at various doses. Various parameters such as changes in body weight, liver function test, kidney function test including serum creatinine levels, uric acid, urea, various ions such as K⁺, Ca²⁺, Mg²⁺, Na⁺ along with cytosolic enzyme alanine aminotransferase which is usually present in liver and enzyme aspartate aminotransferase which is present in mitochondria of tissues such as heart and kidney were measured post-treatment. Nephrotoxicities were induced in this study by administration of intraperitoneal injection of sodium oxalate which were indicated by elevated levels of blood urea and serum creatinine. It was observed that in contradiction to PAA treated group, groups treated with two doses of PAB showed attenuation in the levels of serum creatinine and blood urea significantly indicating the nephroprotective effect of PAB. Elevated levels of these enzymes are considered as indicator of hepatotoxicity. It was observed that group treated with PAA had elevated levels of ALT (27%) and PAL (31–51%) in serum indicating that PAA is ineffective against toxicity induced by oxalate and did not show hepatoprotection. Overall data in the study suggested that PAB when administered to rats in which lithiasis was induced by sodium oxalate, reduced and prevented the urinary stones growth, which supported the traditional usage of PA as an antiurolithiatic agent. Mechanism which leads to different activities of two extracts need to be explored which will further prove the antiurolithiatic property of PA extracts.

### Protection against Ulcerative Colitis

Ulcerative colitis affects colon and rectum and is classified as inflammatory bowel disease (IBD) which occurs recurrently and is chronic when relapsed in intestine. Clinical symptoms include diarrhea, stool with blood, pain in abdomen and loss in body weight. Two most common drugs for treatment of colitis are mesalazine and sulfasalazine. These drugs are associated with unwanted effects on male fertility along with adverse effect of sulfasalazine including vomiting, hypospermia, hepatitis, pneumonitis, hemolytic anemia and chronic nephrosis andencephalitis. It has been observed that sometimes treatment with sulfasalazine exacerbates colitis which results in diarrhea, abdominal cramps and unaiseas. These side effects can be overcome by medicinal plant based therapeutics which could have less or no adverse side effects. It is well established fact that oxidative stress contributes majorly to tissue injury and fibrosis which are characteristic features of IBD. Recently a research group has performed *in vivo* assays to evaluate the effect of PA methanolic extract (PAM) against acetic acid-induced ulcerative colitis in mice. The study was based on the fact that during ulcerative colitis, increased levels of superoxide and nitric oxide lead to peroxynitrite formation which causes oxidation of lipids, proteins and DNA, reducing these parameters to normal levels by overcome by medicinal plant based therapeutics which could have less or no adverse side effects. It is well established fact that oxidative stress contributes majorly to tissue injury and fibrosis which are characteristic features of IBD. Recently a research group has performed *in vivo* assays to evaluate the effect of PA methanolic extract (PAM) against acetic acid-induced ulcerative colitis in mice. The study was based on the fact that during ulcerative colitis, increased levels of superoxide and nitric oxide lead to peroxynitrite formation which causes oxidation of lipids, proteins and DNA, reducing these parameters to normal levels by **Table 2: Classes of phytochemicals present in the *Paronychia argentea*.

| Classes of Phytochemicals | Solvent | - = absence; + = presence; ++ = abundant |
|--------------------------|---------|------------------------------------------|
| Sterols and Terpenoids   | CHCl₃   | +++                                     |
|                          | EtOH    | ++                                      |
|                          | H₂O     | Nil                                     |
|                          | CHCl₃   | Nil                                     |
| Flavonoids               | EtOH    | +                                       |
|                          | H₂O     | ++                                      |
|                          | CHCl₃   | ++                                      |
| Phenolics                | EtOH    | +++                                     |
|                          | H₂O     | +++                                     |
|                          | CHCl₃   | +++                                     |
| Tannins                  | EtOH    | +++                                     |
|                          | H₂O     | +++                                     |
|                          | CHCl₃   | +++                                     |
| Saponins                 | EtOH    | +++                                     |
|                          | H₂O     | +++                                     |
|                          | CHCl₃   | +++                                     |
| Reducing compounds       | EtOH    | +++                                     |
|                          | H₂O     | +++                                     |
|                          | CHCl₃   | +++                                     |
| carbohydrates            | EtOH    | +++                                     |
|                          | H₂O     | +++                                     |
| Volatile oils            | EtOH    | +++                                     |
|                          | H₂O     | +++                                     |

+ Faint, ++ clear, +++ very clear, ++++ highly intense
sedimentation rate (ESR) count which is being used as a marker for inflammatory diseases was found to be reduced to normal levels post-treatment with PAM. Serum C-reactive protein levels, another marker for inflammation was also found to be reduced in treated group when compared with colitis group. As mentioned above, free radicals and reactive oxygen species were reported in ulcerative colitis along with lipid peroxidation. Malondialdehyde (MDA) is the product of lipid peroxidation, it was observed that group of mice treated with PAM showed reduced levels of MDA when compared with colitis control group. Data suggested that efficacy of PA against ulcerative colitis was mediated by anti-oxidant and anti radical scavenging ability. Along with above parameters, reduced glutathione (GSH) levels in the colonic tissue of colitis mice was found. Post-treatment with PAM, significant increase in GSH levels was observed when compared with UC control groups. This data further adds that anti-inflammatory effect of PA could be due to its ability to release glutathione.

Protection from the oxidative stress

It has been well proven that pesticide chemicals can lead to oxidative stress through generation of free radicals and it can also alter the antioxidant levels of the enzymes showing free radical scavenging activity. Chlorpyrifos (CE) is one such pesticide used in farms (Figure 3). Its toxicity is mediated by inhibiting acetyl cholinesterase (AChE) along with other mechanisms. This chemical has got ability to modify endogenous antioxidants like SOD, GPX and GSH which may cause oxidative stress in tissues and can significantly reduce the activities of glutathione (GSH), catalase (CAT) and glutathione -S -transferase (GST). Many plant extracts have proven anti-oxidant activity which boosts immune response and many studies have shown that flavonoids have antioxidants property. PA has a high flavonoid content, this indicates its antioxidant property. Zama et al. have elucidated the role of PA in protection from the oxidative stress caused by CE. Pregnant albino Wistar rats were used for the study and these were orally fed with pesticide and PA extract. Plasma and tissue malondialdehyde (MDA), GSH and erythrocyte superoxide dismutase (SOD) activities were calculated. MDA levels were estimated in plasma and different organs (liver, kidney, brain, placenta and in the fetuses and their livers) as an indicator of lipid peroxidation (LPO). Effect of CE and butanolic plant extract (PAB) on fetus was observed. Groups treated with CE showed significant increase in lipid peroxidation levels pesticide which was attenuated by the plant extract (PAB). Also, CE caused a significant decrease in antioxidant enzyme activity and this effect was partially reversed in groups treated with the PAB. The decrease in LPO levels and the increase in GSH and SOD enzyme activities post treatment with PAB validated its antioxidant property.

Anti-bacterial efficacy

Bacterial community both gram positive and gram negative are the major causative agent for various human infections. Resistance is developing to available antimicrobials limiting the options for treatment. The prevalence of multi-drug resistance of bacterial strains necessitates new classes of anti-bacterials which can overcome resistance. PA has been tested for its antimicrobial potential, since plant extracts and molecules derived from them can be a safe alternative. Antimicrobial potential of aqueous and ethanolic extract of Paronychia argentea Lam. (Caryophyllaceae) was studied against six Gram negative bacteria and one Gram positive bacterium. It was observed that ethanol extract of PA exhibited the highest antimicrobial potential against most of the tested bacteria except for Klebsiella pneumoniae and Escherichia coli. Another most common bacterial infection is by Helicobacter pylori which has been proven to be the major factor in gastric cancer, chronic active gastritis, duodenal ulcer, gastric ulcer and gastric lymphoma. The available treatment regimen for H. pylori includes the combination of antibiotics along with agents which can suppress acid formation. With the prevalence of drug resistance along with side effects and cost of the available treatment, search for new drugs with reduced side effects is the need. A study conducted using PA extract has shown that PA has a moderate efficacy against H. pylori. Another study has shown the efficacy of crude saponins extracted from the aerial parts of PA for the antioxidant, antimicrobial and synergistic effects with antibiotics. The results of minimum inhibitory concentration showed that saponins-rich extract of PA was found to effective against the many Candida strains and Gram-positive bacteria. Moreover, it was found that the combination of saponins rich extract and classical antibiotics exhibited synergistic role against resistant bacteria and Candida.

Alpha amylase inhibitory activity of Paronychia argentea

Various medicinal plants are in use in traditional medicines for their hypoglycemic efficacy. Hypoglycemic activity of many such plants has been proven in vivo using animal models. The mechanism for hypoglycaemic potential of many traditional plants has not yet been explored. The hypoglycaemic effect of the plant extracts could be due to decreased absorption of ingested sugars. This could be possible by inhibition of enzymes which degrade complex carbohydrates. One such enzyme Alpha amylase has been evaluated as a prospective target for controlling diabetes since long. First alpha glucosidase (alpha amylase as well) clinically used was acarbose which was obtained long screening program for glucosidase inhibitors and was significantly efficient in controlling blood glucose. However, it was also associated with side effects such as flatulence. Moreover, it has been well established that alpha amylase inhibitors have better efficacy than alpha glucosidase inhibitors, since they do not lead to the accumulation of maltose and oligosaccharides in the gut. Based on these facts a study was conducted in Jordan to identify new alpha amylase inhibitors and there mechanism of action for the hypoglycemic efficacy. It was found that PA dried crude extract exhibited significant (more than 80%) alpha amylase inhibitory activity. This data supported the hypoglycaemic activity of PA mediated by inhibition of alpha amylase activity which was later on contradicted by in vivo and in vitro studies as explained in next section. The activity of PA was attributed to high flavonoid components in it.

Hypoglycemic activity of PA

PA has been reported to have high content of the flavonoidsisorhamnetin, quercetin and luteolin. Various flavonoids aglycons and glycosides have been explored for their hypoglycemic activity. A study was designed to evaluate the effect of PA on the levels of blood sugar, when crude extract was administered intranasal in the rabbits. This mode of drug administration assures rapid the rapid absorption of the drug and quick beginning of the therapeutic action. It was observed that 1% aqueous extract of PA along with Pluronic F127 (as drug delivery system) at a concentration of 5% (w/w) did not show any decrease in blood sugar levels. The data suggests that this study need to be further carried out using repeated administration of the extracts, since PA is still widely used in Jordan for hypoglycemic efficacy. Another study was conducted using inbred male Fisher rats in which diabetes was induced by streptozotocin. It was observed that PA has no hypoglycemic effect onstreptozotocin-induced diabetic or normal rats. This data which is totally different from the traditional medicinal use of PA as hypoglycemic agent emphasises the need for comprehensive scientific evaluation of chemical, pharmacological and biological properties of medicinal plants used locally as nearly half of the population still depend on medicines from plant sources. The Pharmacological effects of Paronychia argentea were shown in Table 3. The detailed research on activities of less explored medicinal plants of historical practice will not only enhance the available knowledge but also ascertain efficacy and safety.
**Table 3**: Pharmacological effects of PA.

| Extract tested of Paronychia argentea | In vitro/vivo | Activity |
|--------------------------------------|--------------|----------|
| Aqueous extract (PA) and butanolic extract (PAB) | *In vivo* in Wistar rats | Nephroprotective (PA when administered to rats with NaOx-induced lithiasis, reduced and prevented the growth of urinary stones) |
| PA methanolic extract (PAM) | *In vivo* against acetic acid-induced ulcerative colitis in mice | Protective against Ulcerative Colitis | Evident by decreased levels of inflammatory markers and Malondialdehyde (MDA), product of lipid peroxidation |
| n-butanol extract | *In vivo* in Pregnant albino Wistar rats | Decreased oxidative stress induced by Chlorpyrifos (CE) | Decrease in LPO levels and the increase in GSH and SOD enzyme activities post treatment with PAB validated its antioxidant property |
| Aqueous and ethanolic extract of PA | In vitro | Anti-bacterial efficacy | majority of Candida strains and Gram-positive bacteria, *H. Pylori* |
| Crude extract of PA | | Alpha amylase inhibitory activity | |
| Aqueous extract of PA | *In vitro* and *In vivo* in streptozocine-induced diabetic rats | Hypoglycemic activity of PA | In contrary to traditional usage, no hypoglycemic efficacy was observed |

**CONCLUSION**

This review was focussed on the morphology, habitat, photochemistry, traditional medicinal usage and pharmaceutical evaluation of Paronychia argentea. Available literature showing various bioactivities of PA has strengthened its medicinal value. However, few studies have also given contradictory data when compared with traditional usage of the plant. As in the case of alpha-amylase inhibitory efficacy of PA, it was observed that PA inhibits alpha-amylase activity but later on it was proven that PA does not have a hypoglycemogenic effect. This emphasizes the need for proper investigation of the mechanism of action, toxicity evaluation and clinical studies of this plant. Further detailed studies of the structure of compounds obtained from the extract of PA could lead to synthesis of new therapeutic molecules which could serve as safe and better alternative.

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Nil.

**CONFLICT OF INTERESTS**

None.

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